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ABOUT COVER

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The primary aim of *World Journal of Gastrointestinal Surgery* (WJGS, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, etc.

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Outcome of split liver transplantation vs living donor liver transplantation: A systematic review and meta-analysis

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Abstract

BACKGROUND

The outcomes of liver transplantation (LT) from different grafts have been studied individually and in combination, but the reports were conflicting with some researchers finding no difference in both short-term and long-term outcomes between the deceased donor split LT (DD-SLT) and living donor LT (LDLT).

AIM

To compare the outcomes of DD-SLT and LDLT we performed this systematic review and meta-analysis.

METHODS

This systematic review was performed in compliance with the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines. The following databases were searched for articles comparing outcomes of DD-SLT and LDLT: PubMed; Google Scholar; Embase; Cochrane Central Register of Controlled Trials; the Cochrane Database of Systematic Reviews; and *Reference Citation Analysis* (<https://www.referencecitationanalysis.com/>). The search terms used were: "liver transplantation;" "liver transplant;" "split liver transplant;" "living donor liver transplant;" "partial liver transplant;" "partial liver graft;" "ex

vivo splitting;" and "in vivo splitting."

RESULTS

Ten studies were included for the data synthesis and meta-analysis. There were a total of 4836 patients. The overall survival rate at 1 year, 3 years and 5 years was superior in patients that received LDLT compared to DD-SLT. At 1 year, the hazard ratios was 1.44 (95% confidence interval: 1.16-1.78; $P = 0.001$). The graft survival rate at 3 years and 5 years was superior in the LDLT group (3 year hazard ratio: 1.28; 95% confidence interval: 1.01-1.63; $P = 0.04$).

CONCLUSION

This meta-analysis showed that LDLT has better graft survival and overall survival when compared to DD-SLT.

Key Words: Deceased donor liver transplantation; Living donor liver transplantation; Split liver transplantation; Overall survival; Graft survival; Acute rejection

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Core Tip: This meta-analysis is one of the few studies in the literature to compare the deceased donor split liver transplantation (DD-SLT) and living donor liver transplantation (LDLT) patients in terms of clinical outcomes. Although this study had some limitations, this meta-analysis showed that LDLT has better graft survival and overall survival compared to DD-SLT. The allograft in LDLT also had superior outcomes compared to DD-SLT in terms of acute rejection.

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INTRODUCTION

Liver transplantation (LT) is the treatment of choice for end stage liver diseases as well as selected liver malignancies and metabolic disorders. Since LT became accepted as a therapeutic procedure, there was an increase in the number of patients listed to receive LT. This resulted in a significant organ shortage with high waiting list mortality[1,2]. To alleviate the organ shortage, efforts were made to increase donor pool. Some of these efforts include: donation after cardiac death; extended criteria donors; deceased donor-split LT (DD-SLT); living donor LT (LDLT); and domino or sequential LT.

The first DD-SLT was conducted in 1988 by Pichlmayr *et al*[3] when they split the liver into two grafts: one for a child (left lateral segment) and the other for an adult (extended right trisegments). Bismuth *et al*[4] in 1989 reported another case of SLT for 2 patients with acute liver failure. The first series was reported in 1990 by Emond *et al*[5] of the University of Chicago. They described their experience with nine DD-SLT procedures in 18 pediatric and adult recipients. Shortly after the first DD-SLT, Raia *et al*[6] and Strong *et al*[7] conducted the first reported LDLT. Since then, both types of LT have gained acceptance, with DD-SLT now being utilized for two carefully selected adults.

The outcome of LDLT and SLT have been studied individually and in combination, but the reports were conflicting with some researchers finding no difference in both short-term and long-term outcomes between the two types of LT[8-10]. However, there are some reports of superiority of one over the other[11-13]. One of the common themes in all these reports is the small sample size, which may serve as a major limitation to any conclusion drawn from these studies. We aimed to perform this systematic review and meta-analysis to compare the outcomes of DD-SLT and LDLT.

MATERIALS AND METHODS

This systematic review was performed in compliance with the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines. The protocol for this systematic review was prospectively registered on the International Prospective Register of Systematic Reviews, PROSPERO (CRD42022350273). This study did not include patient participation. Therefore, ethical clearance from the institutional review board and patient informed consent were not sought.

Search strategies

Two reviewers (SA and FA) independently searched several databases for articles comparing outcomes of LDLT and DD-SLT. The databases were: PubMed; Google Scholar; Embase; Cochrane Central Register of Controlled Trials; the Cochrane Database of Systematic Reviews; and *Reference Citation Analysis* (<https://www.referencecitationanalysis.com/>). The search was conducted from July 15, 2022 through August 3, 2022. The search terms used were "liver transplantation;"

“liver transplant;” “split liver transplant;” “living donor liver transplant;” partial liver transplant;” “partial liver graft;” “ex vivo splitting;” and “in vivo splitting.” Boolean logic was used to combine the keywords. Related articles and reference lists were searched to avoid omission. In case of conflict between the two reviewers, a third reviewer resolved the conflict.

Eligibility criteria

Studies that fulfilled the following criteria were included for the review: (1) Studies published from 1990 to date; (2) Studies that compared the outcomes of DD-SLT and LDLT; and (3) Studies published in English. Exclusion criteria were as follows: (1) Editorials and commentaries; (2) Publications in other languages apart from English; (3) Lack of relevant data or insufficient data; and (4) Total study population less than 10 patients.

Quality assessment and risk of bias assessment

To assess the risk of bias, two authors analyzed the quality of each included study independently using the NIH Quality Assessment Tool for Case-Control Studies. The maximum score on this scale was 12. Studies were considered good when scored ≥ 9 , fair when scored 6-8 and poor when scored ≤ 5 . The risk of publication bias was assessed by inspection of funnel plot for symmetry.

Data extraction

Data were extracted by two reviewers separately (AA and MN). The data extracted include: name of authors; year of publication; number of patients included in DD-SLT and LDLT; age of recipients in each group; sex of recipients in each group; model for end-stage liver disease score of the recipients in each group; cold ischemic time (CIT) in each group; overall biliary complications; hepatic artery thrombosis; portal vein thrombosis; early postoperative mortality; acute graft rejection; and 1-year, 3-year and 5-year overall patient and graft survival. Disagreements between reviewers were discussed with a third reviewer (IUG) to reach an agreement.

Outcome

The primary outcome we considered in this meta-analysis was patient and graft survival. Secondary outcomes include CIT in each group, overall biliary complications, hepatic artery thrombosis, portal vein thrombosis, early postoperative mortality and acute graft rejection.

Statistical analysis

All statistical analyses were performed using RevMan software (version 5.4.1). For dichotomous variables, the pooled relative risk (RR) was calculated with 95% confidence interval (CI). For continuous variables, the weighted mean difference or standardized mean difference (SMD) with 95% CI was calculated. We used a fixed-effects model to calculate the pooled effect sizes if the data were not significantly heterogeneous. Otherwise, a random-effects model was used. Heterogeneity was evaluated by I^2 statistics. $I^2 > 50\%$ was considered as statistically significant heterogeneity. Sensitivity analysis was used by omitting each included study in the meta-analysis to identify the main source of heterogeneity. Standard deviation was computed from standard error, CI or from P values if it was not given directly in the articles. If the article included did not provide the mean value, we used the Wan *et al*[14] method of computing mean from median and range. In the survival analysis, the log hazard ratio and variance were obtained by the Tierney *et al*[15] method of computing the percentage survival at a given time. Publication bias was evaluated using the funnel plot and Egger's test if 10 or more studies were included in the meta-analysis of a particular outcome as recommended by the Cochrane handbook.

RESULTS

Characteristics of included studies

During the initial search, 3723 references were identified. Among the identified references, there were 1711 duplicates and 1989 unrelated articles, and these were excluded (Figure 1). After exclusion, there were 23 remaining articles, and these were retrieved for complete assessment. Thirteen references were excluded because the study populations were different. Ten studies[16-25] were included for the data synthesis and meta-analysis. The studies included were all retrospective studies dated between 2005 and 2022. Overall, there were a total of 4836 patients with 3006 of them undergoing LDLT, while 1830 received DD-SLT. Five of the studies were conducted in the United States[17,19,21-23], and the remaining five studies were conducted in Italy[20], Belgium[18], South Korea[25], France[24] and Iran[16].

Study quality

Four of the studies were of good quality, while six were of fair quality based on the NIH Quality Assessment Tool for Case-Control. Details of selected studies were displayed in Table 1.

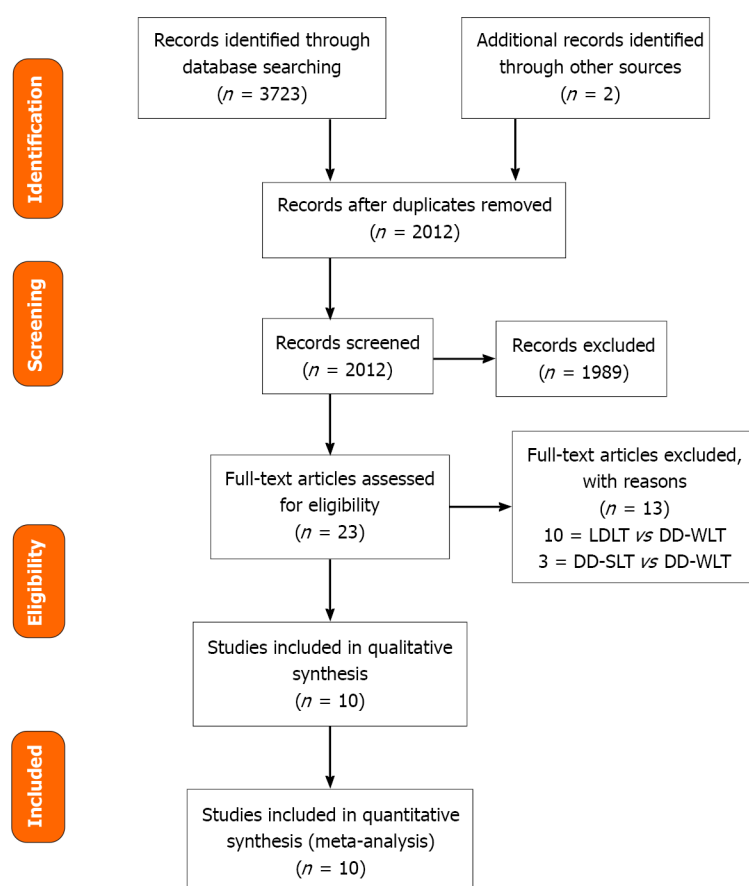
Sociodemographic characteristics and baseline liver function

The two groups did not show any statistical significance in age distribution (SMD: 0.30; 95%CI: 0.44-1.04; $P = 0.43$). The sex distribution however differed between the two groups with more males receiving DD-SLT compared to LDLT (RR: 0.81; 95%CI: 0.71-0.93; $P = 0.003$). There was no statistically significant difference between the two groups regarding

Table 1 Studies included in the meta-analysis

Ref.	Year	Sample size		Quality assessment score	Quality
		LDLT	DD-SLT		
Dalzell <i>et al</i> [17]	2022	403	508	9	Good
Sebagh <i>et al</i> [24]	2006	38	20	8	Fair
Saidi <i>et al</i> [23]	2011	1715	557	9	Good
Yoon <i>et al</i> [25]	2022	56	63	7	Fair
Giacomoni <i>et al</i> [20]	2005	18	9	7	Fair
Humar <i>et al</i> [22]	2008	69	31	9	Good
Darius <i>et al</i> [18]	2014	203	47	8	Fair
Diamond <i>et al</i> [19]	2007	360	261	9	Good
Bahador <i>et al</i> [16]	2009	54	20	8	Fair
Hong <i>et al</i> [21]	2009	90	181	7	Fair

DD-SLT: Deceased donor split liver transplantation; LDLT: Living donor liver transplantation.



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Figure 1 Preferred Reporting Items for Systematic Review and Meta-Analysis flow chart for literature search and study inclusion. DD-SLT: Deceased donor split liver transplantation; DD-WLT: Deceased donor whole liver transplant; LDLT: Living donor liver transplantation.

model for end-stage liver disease/pediatric end-stage liver disease score (SMD: 0.35; 95%CI: 0.20-0.91; $P = 0.21$). The CIT was significantly different between the two groups, with the DD-SLT group having a longer CIT (SMD: 8.57; 95%CI: 0.05-17.09; $P < 0.001$).

Primary outcome

Overall survival: The overall survival rate at 1 year, 3 years and 5 years were compared and reported in five studies[17,19,20,23,25], five studies[17,19,22,23,25] and four studies[17,22,23,25], respectively. The overall survival at 1 year, 3 years and 5 years was superior in patients that received LDLT compared to DD-SLT. At 1-year, the hazard ratio was 1.44 (95%CI: 1.16-1.78; $P = 0.001$). The detailed HR and P value are presented in Figure 2. We did not assess publication bias as less than 10 studies were included in the meta-analysis.

Graft survival: The graft survival rate at 1 year, 3 years and 5 years were compared and reported in seven studies[17,19,20,22-25], five studies[17,19,22,23,25] and three studies[22,23,25], respectively. Graft survival between the two groups was not significantly different between the two groups at 1 year (HR: 1.11; 95%CI: 0.92-1.33; $P = 0.27$). However, at 3 years, the graft survival in the LDLT group was superior to graft survival in the DD-SLT group (HR: 1.28; 95%CI: 1.01-1.63; $P = 0.04$). The difference was not sustained as the graft survival at 5 years showed no difference between DD-SLT and LDLT (HR: 1.46; 95%CI: 0.83-2.58; $P > 0.05$).

The detailed meta-analysis is presented in Figure 3. There was significant heterogeneity among the studies used for meta-analysis of 5-year graft survival with $I^2 = 71\%$. The main source of heterogeneity was the study by Saidi *et al*[23]. After eliminating this study from the meta-analysis, the heterogeneity vanished with $I^2 = 0\%$. We also observed a significant difference in the 5-year graft survival in favor of those that received LDLT (HR: 1.98; 95%CI: 1.20-3.26; $P = 0.007$). We did not assess publication bias as less than 10 studies were included in the meta-analysis.

Secondary outcomes

Primary non-function: Primary non-function (PNF) assessment was completed in three studies[17,21,22] comprising 720 patients in the DD-SLT group and 562 patients in the LDLT group. PNF occurred among 20 patients in DD-SLT, but in the LDLT group only 11 patients developed PNF. There was no significant heterogeneity between the studies with $I^2 = 0\%$. Therefore, the fixed effect was used in estimating pooled effect. The pooled RR was 1.13 (95%CI: 0.57-2.25; $P = 0.72$), which was not statistically significant. We did not assess publication bias as less than 10 studies were included in the meta-analysis.

Vascular complications: Hepatic artery thrombosis was reported in seven studies[16,17,19-21,24] consisting of 1062 patients in the DD-SLT group and 1019 patients in the LDLT group. Hepatic artery thrombosis occurred in 56 patients in the DD-SLT group, but in the LDLT group 66 patients developed hepatic artery thrombosis. There was no significant heterogeneity between the studies with $I^2 = 0\%$. Therefore, the fixed effect was used in estimating pooled effect. The pooled RR was 0.90 (95%CI: 0.64-1.26; $P = 0.53$), which was not statistically significant. We did not assess publication bias as less than 10 studies were included in the meta-analysis.

Portal vein thrombosis was reported in four studies[17,19,21,25] comprising 1013 patients in the DD-SLT group and 909 patients in LDLT group. Portal vein thrombosis occurred in 36 patients in the DD-SLT group and among 43 patients in the LDLT group. The heterogeneity between studies was not significant with $I^2 = 0\%$, and the fixed effect was used to estimate pooled effect. The pooled RR was 0.91 (95%CI: 0.59-1.38; $P = 0.65$), which was not statistically significant. We did not assess publication bias as less than 10 studies were included in the meta-analysis.

Retransplantation: The rate of re-LT was reported in five studies[17,19-21,24] consisting of 979 patients in the DD-SLT group and 909 patients in the LDLT group. Re-LT was needed in 82 patients in the DD-SLT group, and 71 patients needed re-LT in the LDLT group. There was no significant heterogeneity between studies with $I^2 = 0\%$, and the fixed effect was used to estimate pooled effect. The pooled RR was 0.97 (95%CI: 0.72-1.31; $P = 0.84$). We did not assess publication bias as less than 10 studies were included in the meta-analysis.

Acute rejection

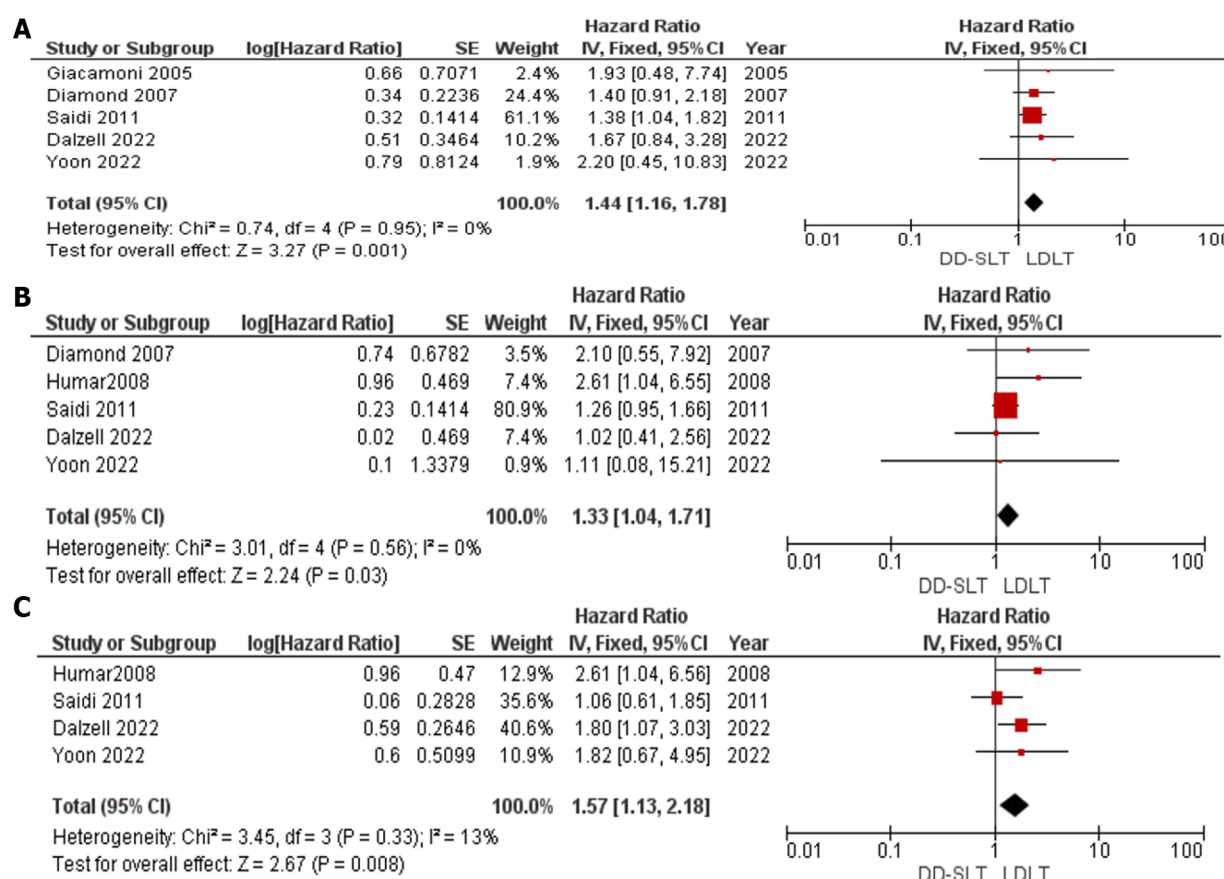
Acute rejection was compared between the two groups in three studies[16,22,24] comprising 71 patients in the DD-SLT group and 161 patients in the LDLT group. Acute rejection was observed in 17 patients among the DD-SLT group and 22 patients in the LDLT group. There was no heterogeneity between the studies with the $I^2 = 0\%$. The difference was significant (RR: 1.75; 95%CI: 1.04-2.94; $P = 0.04$). The detailed meta-analysis is presented in Figure 4. We did not assess publication bias as less than 10 studies were included in the meta-analysis.

Biliary complications

Eight studies[16-21,24,25] compared biliary complications between the DD-SLT and LDLT groups. In the studies, 1109 patients received DD-SLT and 1222 patients received LDLT. There was significant heterogeneity between the studies. Therefore, the random effect was used to test for the overall effect. The pooled RR was 0.86 (95%CI: 0.49-1.52). There was no difference between the two groups ($P = 0.60$). We did not assess publication bias as less than 10 studies were included in the meta-analysis.

Postoperative mortality

Early postoperative mortality within 3 mo was reported in four studies[19,20,24,25] consisting of 353 patients in the DD-SLT group and 472 patients in the LDLT group. There was no heterogeneity between the studies with $I^2 = 0\%$. There was a significant difference in the mortality between the two group with the DD-SLT group having more mortality (RR: 1.95; 95%CI: 1.11-3.42; $P = 0.02$). We did not assess publication bias as less than 10 studies were included in the meta-analysis.



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Figure 2 Forest plot for the 1-year, 3-year and 5-year overall survival. A: 1 year; B: 3 year; C: 5 year. CI: Confidence interval; DD-SLT: Deceased donor split liver transplantation; LDLT: Living donor liver transplantation; SE: Standard error.

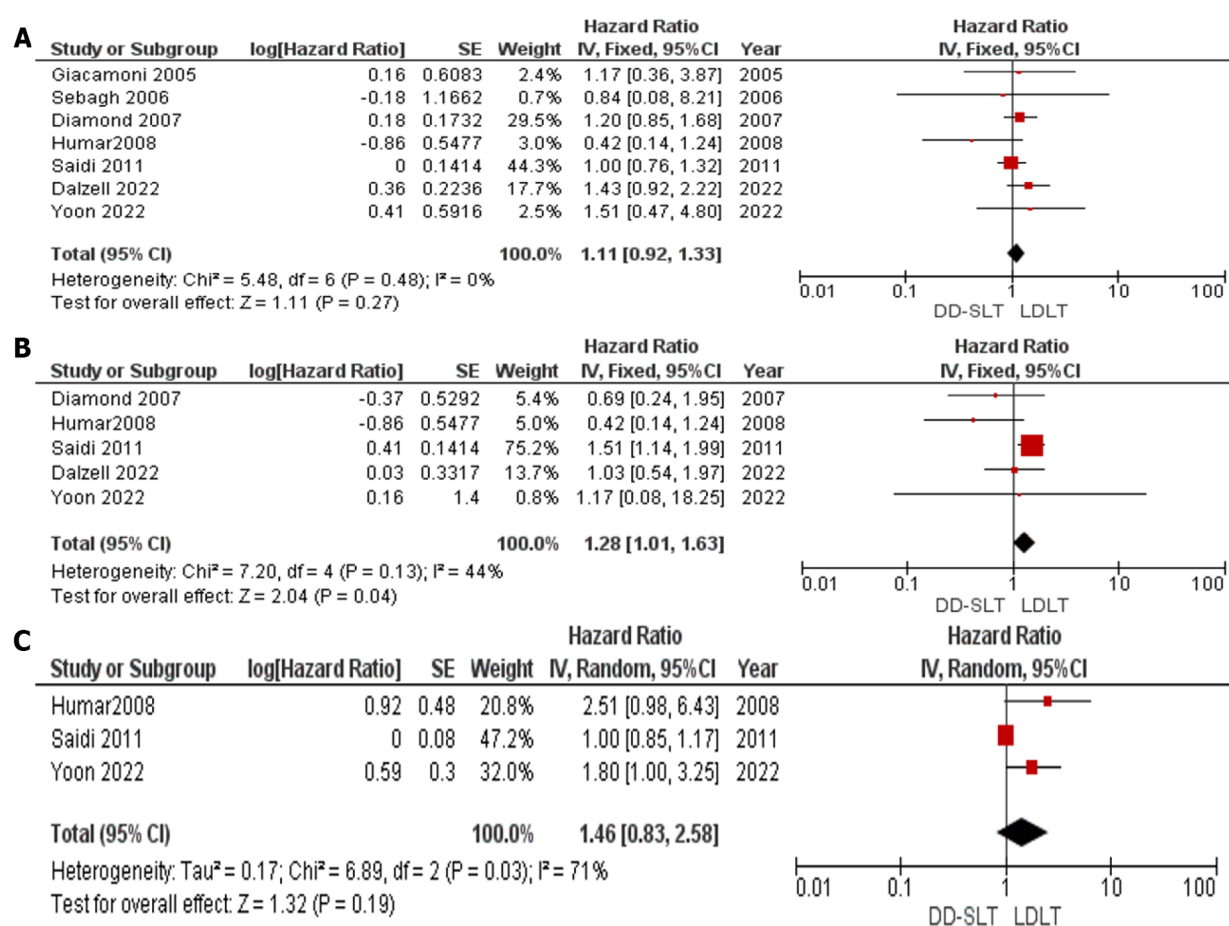
DISCUSSION

In this meta-analysis, we compared the short-term and long-term outcomes of LT between those that received LDLT and those that received DD-SLT. The primary outcome we compared was overall survival, and the meta-analysis revealed that patients that received LDLT had a superior overall survival compared to those that received DD-SLT. At 1-year post-LT, there was a difference in the overall survival between the two groups with an HR of 1.44 (95%CI: 1.16-1.78; $P = 0.001$). This superiority was sustained through the 3rd and 5th years after LT. Our findings are similar to the meta-analysis conducted by Barbetta *et al* [26] among pediatric patients receiving partial liver allograft. These findings may be attributed to the fact that most LDLT procedures are elective. Therefore, the recipients are of better health status. In addition, there is a shorter CIT in LDLT. Gavriilidis *et al* [8] reported contrasting findings in their meta-analysis of adults receiving LDLT vs DD-SLT. Their findings may not be significant because only three studies were analyzed after 1 year and two studies were analyzed after 3 years and 5 years. The included studies also exhibited marked heterogeneity as I^2 was $> 50\%$.

Graft survival showed a complex pattern in our meta-analysis. The graft survival showed superiority in the LDLT group after 1 year, 3 years and 5 years based on the forest plots. This difference was only significant at 3 years. There was marked heterogeneity between studies used for the meta-analysis of the 5-year graft survival with $I^2 = 71\%$. The main source of heterogeneity was the study by Saidi *et al* [23]. After eliminating this study from the meta-analysis, the heterogeneity vanished with $I^2 = 0\%$. We also observed a significant difference in the 5-year graft survival in favor of those that received LDLT (HR: 1.98; 95%CI: 1.20-3.26; $P = 0.007$). The findings of Gavriilidis *et al* [8] showed no significant differences in graft survival between the two groups at 1 year, 3 years and 5 years.

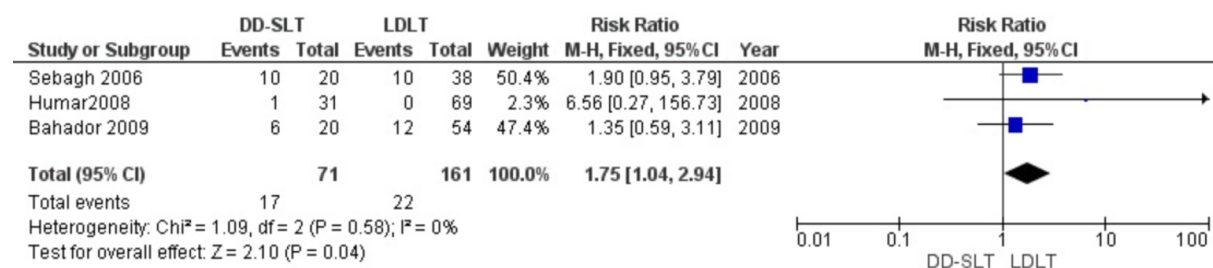
We compared early vascular and technical complications like hepatic artery thrombosis, portal vein thrombosis and biliary complications after LT between the groups that received DD-SLT and LDLT. Our findings revealed there were no significant differences between the two groups regarding these complications. These findings were also presented in the meta-analysis conducted by Gavriilidis *et al* [8]. Similarities in these outcomes between LDLT and DD-SLT were a result of the procedures being similar with the primary difference being the status of the donor. In LDLT, the procedure is performed on live patients and only a part of the liver is harvested for use on a single recipient. While in DD-SLT, the procedure is performed on a brain dead donor, and the liver is split into two parts and received by two recipients.

Early post-LT mortality occurring within 3 mo of LT was also compared between recipients of DD-SLT and recipients of LDLT. Our meta-analysis revealed that recipients of LDLT had a better outcome with less early mortality compared to DD-SLT. The mortality pattern may reflect the pre-LT status of the patients and that most DD-SLT procedures were



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Figure 3 Forest plot for the 1-year, 3-year and 5-year graft survival. A: 1 year; B: 3 year; C: 5 year. CI: Confidence interval; DD-SLT: Deceased donor split liver transplantation; LDLT: Living donor liver transplantation; SE: Standard error.



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Figure 4 Forest plot for acute rejection. DD-SLT: Deceased donor split liver transplantation; CI: Confidence interval; LDLT: Living donor liver transplantation.

performed as emergency surgeries.

One of the causes of graft loss in the setting of LT is acute rejection. Shaked *et al*[27] reported clinically evident acute rejection in 26% of 593 patients who received LT. In the same study, biopsy proven acute rejection was seen in 27% of the study population. Our meta-analysis compared acute rejection between DD-SLT and LDLT, and we found that LDLT was associated with less acute rejection episodes. This is similar to the findings of Barbetta *et al*[26] in a meta-analysis comparing outcomes of LT among pediatric recipients of partial liver allografts. The reasons for less acute rejection in the LDLT group may include the following: donor organs with minimal exposure to brain death associated stress; minimal injuries associated with prolonged CIT; and human leukocyte antigen matching among biologically related individuals.

Another cause of graft loss after LT is PNF, which may ultimately require re-LT. The incidence of PNF after LT has been reported as 2.2%-3.5%[28,29], but an incidence of up to 27% has been reported by González *et al*[30]. In this meta-analysis, we compared PNF and re-LT between recipients of LDLT and recipients of DD-SLT. Our finding revealed no statistically significant difference between the two groups regarding PNF and re-LT.

This study had a few limitations. The first was that all of the studies included in this study included retrospective case-control studies. However, it is very difficult to resolve this limitation, and designing a prospective study on this subject involves ethical problems. It is unethical not to transplant a patient who has a chance for DD-SLT and to force him to receive LDLT. Conversely, keeping a patient with a chance of LDLT on the waiting list for an academic study is also ethically problematic. Therefore, it does not seem possible to conduct a prospective study on this issue at the present time. Second, since there is no randomization in retrospective studies, it is not expected that the groups will be homogeneous, which we demonstrated in our study.

CONCLUSION

This meta-analysis is one of the few studies in the literature to compare DD-SLT and LDLT patients in terms of clinical outcomes. Although this study has some limitations, this meta-analysis has shown that LDLT has a better graft survival and overall survival compared to DD-SLT. The allograft in LDLT also has a superior outcome compared to DD-SLT in terms of acute rejection.

ARTICLE HIGHLIGHTS

Research background

The outcome of liver transplantation (LT) may be affected by the type of graft implanted in the recipient. The graft may be from a deceased donor or from a living donor. Deceased donor graft may be whole graft or split graft.

Research motivation

To encourage the utilization of deceased donor split LT (DD-SLT) to increase the donor pool in LT.

Research objectives

To perform a systematic review and meta-analysis to compare the outcome of DD-SLT and living donor LT (LDLT).

Research method

This systematic review was performed in compliance with the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines. A search was performed in research databases for articles comparing outcomes of DD-SLT and LDLT. Data were extracted from these studies for meta-analysis.

Research results

Patients that received LDLT had a better overall survival and graft survival.

Research conclusions

This meta-analysis showed that LDLT has a better graft survival and overall survival when compared to DD-SLT.

Research perspectives

To put the study in perspective, the type of graft affected the outcome of LT. Living donor graft has a superior outcome to deceased donor split graft.

FOOTNOTES

Author contributions: Garzali IU, Akbulut S, Aksoy F and Aloun A contributed to the conceptualization; Garzali IU and Aloun A contributed to the formal analysis; Garzali IU and Naffa M performed the methodology and wrote the original draft; Akbulut S and Garzali IU wrote the review and contributed to editing.

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