REVIEW

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Better living donor liver transplantation patient survival compared to deceased donor – a systematic review and meta-analysis

Lourianne Nascimento **CAVALCANTE**[1,2], Renato Macedo Teixeira de **QUEIROZ**[3], Cláudio Luiz da S L **PAZ**[1] and André Castro **LYRA**[1,2]

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ABSTRACT – Background – Deceased donor liver transplantation (DDLT) is the first choice, but living donor transplantation (LDLT) is an alternative to be considered in special situations, such as lack of donated organs and emergencies. So far, there is no consensus on which transplantation method provides better survival and fewer complications, which is still an open point for discussion. **Methods –** This meta-analysis compared the 1, 3, and 5-year patient and graft survival rates of LDLT and DDLT. We included studies published from April-2009 to June-2021 and adopted the generic model of the inverse of variance for the random effect of hazard ratios. The adequacy of the studies was determined using the Newcastle-Ottawa Scale – NOS (WELLS). **Results –** For patient survival analysis, we included a total of 32,258 subjects. We found a statistically significant better survival for the LDLT group at 1, 3 and 5 years, respectively: 1.35 HR (95%CI 1.10–1.66, *P*=0.005), 1.26 HR (95%CI 1.09–1.46, *P*=0.002) and 1.27 HR (95%CI 1.09–1.48, *P*=0.002). Our meta-analysis evaluated a total of 21,276 grafts. In the overall analysis, the 1-year survival was improved in favor of the LDLT group (1.36 HR, 95%CI 1.16–1.60, *P*<0.0001), while the 3-year survival (1.13 HR, 95%CI 0.96–1.33, *P*<0.13), and 5 (0.99 HR, 95%CI 0.74–1.33, *P*<0.96), did not differ significantly. **Conclusion –** This metanalysis detected a statistically significant greater 1-, 3- and 5-years patient survival favoring LDLT compared to DDLT as well as a statistically significant difference better 1-year graft survival favoring the LDLT group.

Keywords – Liver transplantation; living donor liver transplantation; deceased donor liver transplantation.

INTRODUCTION

The success of solid organ transplants may be superior when using organs from living donors[1]. However, it is necessary to take into account and obtain a balance between the risk/benefit ratio of the recipient and donor in several points: non-existent supply of organs from deceased donors; availability of a close relative willing to serve as a donor; a candidate with a potentially fatal disease for which the transplant saves lives or standardizes referrals; and the belief that the psychological benefit experienced by the donor would outweigh the physical damage and risk of mortality associated with the donation[1,2].

Liver transplantation is a complex medical procedure due to many factors. It is associated with several well-known surgery-related complications, as well as immunosuppression issues. Also, there is a worldwide disproportion between donors and recipients. Therefore, many patients perish during the waiting list period awaiting an organ[3,4].

Worldwide, most liver transplants utilize deceased donors. Living donor liver transplantation has emerged as an alternative due to organ shortage[5,6]. One-year and 5-year patient and graft survival rates of liver transplant patients from deceased and living donors might be similar. Nevertheless, there are still some controversies regarding this issue. Post-operative complications appear to occur more frequently after living donor transplantation (LDLT). Hence, there is still no consensus on which of the two types of transplants is better in terms of survival and complications[6].

In this meta-analysis, we compared patient and graft survival rates of living and deceased donor liver transplantation to amplify the knowledge of this relevant issue.

METHODS

Eligibility criteria

We included studies published from April 2009 to June 2021. Inclusion criteria were patients older than 18 years old undergoing liver transplantation who received grafts from living or deceased donors; patient and graft survival comparison. We did not include cases reports and series as well as publications with insufficient data for analysis.

Search strategy

We searched PubMed/Medline databases up to June 30th, 2021, and used Medical Subject Headings (MeSH) descriptors during the process. The systematic review was performed according to PRISMA protocol[7]. All descriptors were organized and crossed according to the boolean operators "and" and "or". The following search strategy was performed: ("transplant recipients"

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[1] Universidade Federal da Bahia, Departamento de Medicina, Salvador, BA, Brasil. [2] Hospital São Rafael – Rede Dor, Salvador, BA, -Brasil. [3] Escola Bahiana de Medicina e Saúde Pública, Salvador, BA, Brasil.
Corresponding author: Lourianne Nascimento Cavalcante. E-mail: lourianne@gmail.com

[MeSH] OR "liver transplantation" [MeSH]) AND ("tissue donors" [MeSH] OR "living donors" [MeSH]) AND ("survival" [MeSH] OR "mortality" [MeSH] OR "mortality" [Subheading]) OR "survival analysis" [MeSH] OR "survival rate" [MeSH] OR "tissue survival" [MeSH] OR "graft survival "[MeSH] OR" Kaplan-Meier estimate "[MeSH]). We also searched the references of the identified studies to retrieve other relevant studies.

Data extraction

Two independent researchers selected the articles by title and abstracts, and we further considered eligible studies for a complete reading. If there was uncertainty about the inclusion of any investigation, we designated another evaluator to do the analysis. We collected the data using a predefined collection form which was then revised.

The variables evaluated in the included studies were the title and principal investigator, year of publication, sample size, the average age of donors and recipients, Model for End-stage Liver Disease (MELD) and Child-Pugh scores pre-transplant, patient and graft survival, early post-surgical complications, and liver disease etiology.

Selection of papers

We researched for papers for the last time on May 30, 2021. In the first stage of the search, we found 344 studies and excluded 284 (74 studies had non-compatible study designs and 210 articles dealt with other topics). We selected 60 studies for full reading and ruled out 32 (31 for not addressing the outcome of interest and one for not being available) (FIGURE 1).

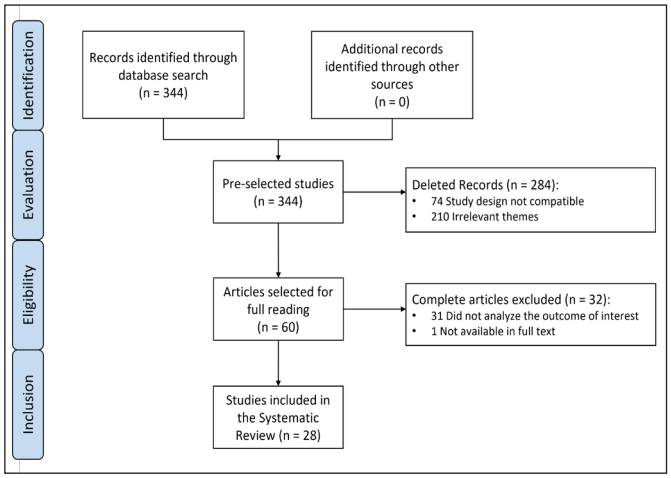

FIGURE 1. Flowchart reporting the process for selection of papers for inclusion in the meta-analysis.

Study risk of bias assessment

The adequacy of the included studies was determined using the Newcastle-Ottawa Scale – NOS (WELLS)[8]. This scale consists of eight questions in three domains, selection, comparability, and exposure or outcome.

Meta-analysis

Survival analysis was determined by extracting hazard ratios (HR) and their respective 95% confidence intervals (95%CI). The studies that did not describe the data of interest descriptively in the text were estimated using Kaplan-Meier graphs when reported; we extracted the information using the online domain application WebPlotDigitizer 4.4[9].

We did the meta-analysis using the Review Manager software (RevMan 5.3. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014)[10]. We adopted the generic model of the inverse of variance for the random effect of HR data. The heterogeneity between the included studies was considered as Cochrane's Q, assuming a level of statistical significance of 0.10 for heterogeneity and the I^2 for inconsistencies in the effect size in the treatments, with I^2 <50% low heterogeneity, ≥50% heterogeneity accepted as substantial, and >75%, high heterogeneity[11]. Visual inspection was adopted, using the improved funnel plot with contour for risk of publication bias when the analysis included ten studies[11]. The asymmetry of the plots was evaluated by the Begg and Egger tests[12,13]. We adopted influence analysis by Baujat plot and leave-one-out analysis to evaluate heterogeneity[13]. We used the software R version 3.5.2 (The R Foundation for Statistical Computing)[14]. The Baujat plot is a graph that diagnoses the contribution of individual studies to heterogeneity[14], while the leave-one-out re-analyzes the results by omitting one study per time. For subgroup analysis, we utilized the following characteristics: recipients' age (<50 years; >50 years).

RESULTS

Patients survival

One, 3- and 5-years survival

A total of 32,258 patients were studied, of which 83% corresponded to the Deceased donor liver transplantation (DDLT) group[3,5,12-19,20-27]. When analyzing the HR distribution in the Forrest plot graphs (FIGURE 2), the results demonstrated a statistically significant better survival for the LDLT group (six studies in the 1-year follow-up, seven papers in the 2-year, and 6 in the 3-year follow-up) (FIGURE 2). Of note, the study of Kulik et al.[19] found a better significant survival for the DDLT group at 1-year follow-up (FIGURE 2.A).

The grouped analyzes showed substantial heterogeneity for survival in 1, 3 and 5 years (I^2=73%, 64% and 72% respectively). In the general analysis, it was observed that, for the periods of 1, 3 and 5 years, there was a greater survival of LDLT patients with, respectively: 1.35 HR (95%CI 1.10–1.66, P=0.005), 1.26 HR (95%CI 1.09–1.46, P=0.002) and 1.27 HR (95%CI 1.09–1.48, P=0.002).

When investigating heterogeneity using the Baujat graphic analysis (FIGURE 3), we identified the study by Xiao et al.[3] as the one that most contributed to the heterogeneity in the 1-year follow-up and as the most influential study on the overall results, while Wong et al.[4] was the one that most contributed for the 3-year analysis. The articles by Wong et al.[4] and Hu et al.[5] were the ones that most contributed to the heterogeneity of the 5-year follow-up, respectively.

Applying the leave-one-out method for sensitivity analysis (FIGURE 4), in the one-year survival analysis, we removed the study by Xiao et al.[3], which explained 32% of the heterogeneity, resulting in a favorable effect for the LDLT group, with 1.45 HR (95%CI 1.21–1.73, I^2=40.9%, P<0.0001). In the 3-year survival analysis, the exclusion of the study by Wong et al.[4] explained 20% of the heterogeneity, but it had little influence on the results initially obtained (1.22 HR, 95%CI 1.08–1, 37, I^2=43.5%). When evaluating the 5-year survival, the withdrawal of the studies by Hu et al.[5] and

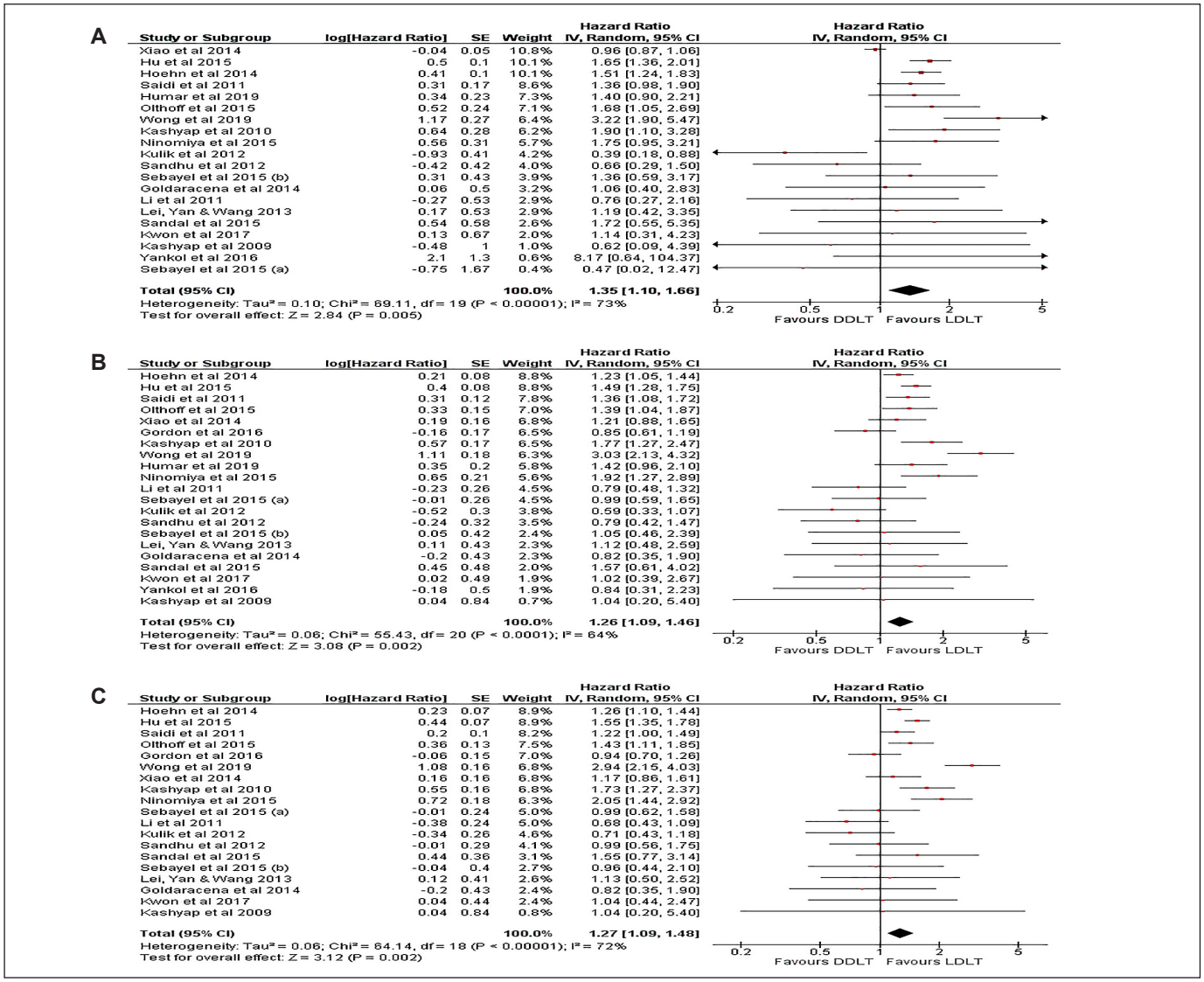

FIGURE 2. Survival of the patient considering the living or deceased donor for liver transplantation: a) 1-year survival, b) 3-years survival and c)-5 years survival.

DDLT: deceased donor liver transplant; LDLT: living donor liver transplant.

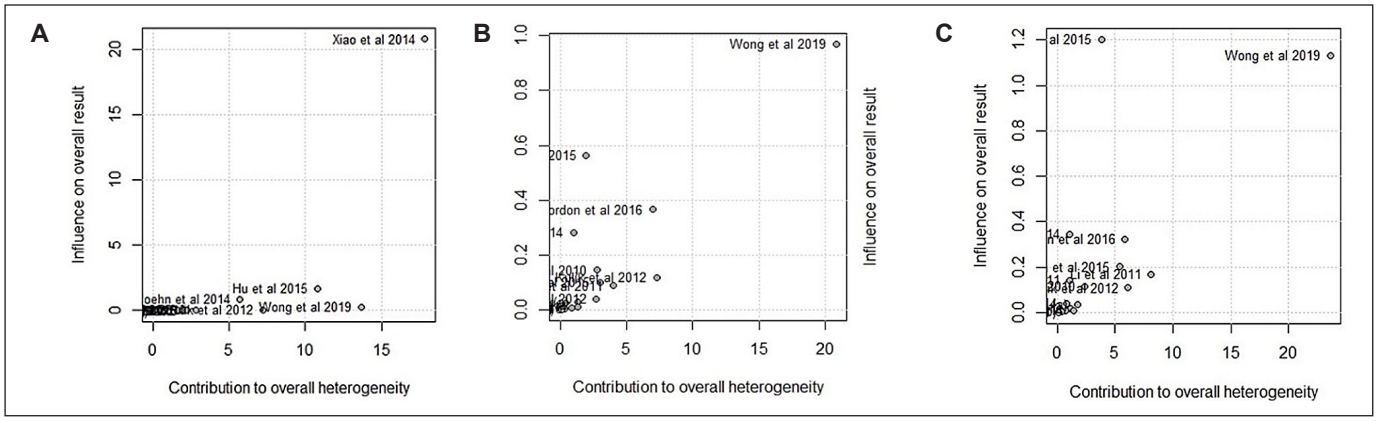

FIGURE 3. Analysis of the heterogeneity by Baujat plot, evaluating survival of patients undergoing liver transplantation: a) 1-year survival, b) 3-years survival and c)-5 years survival.

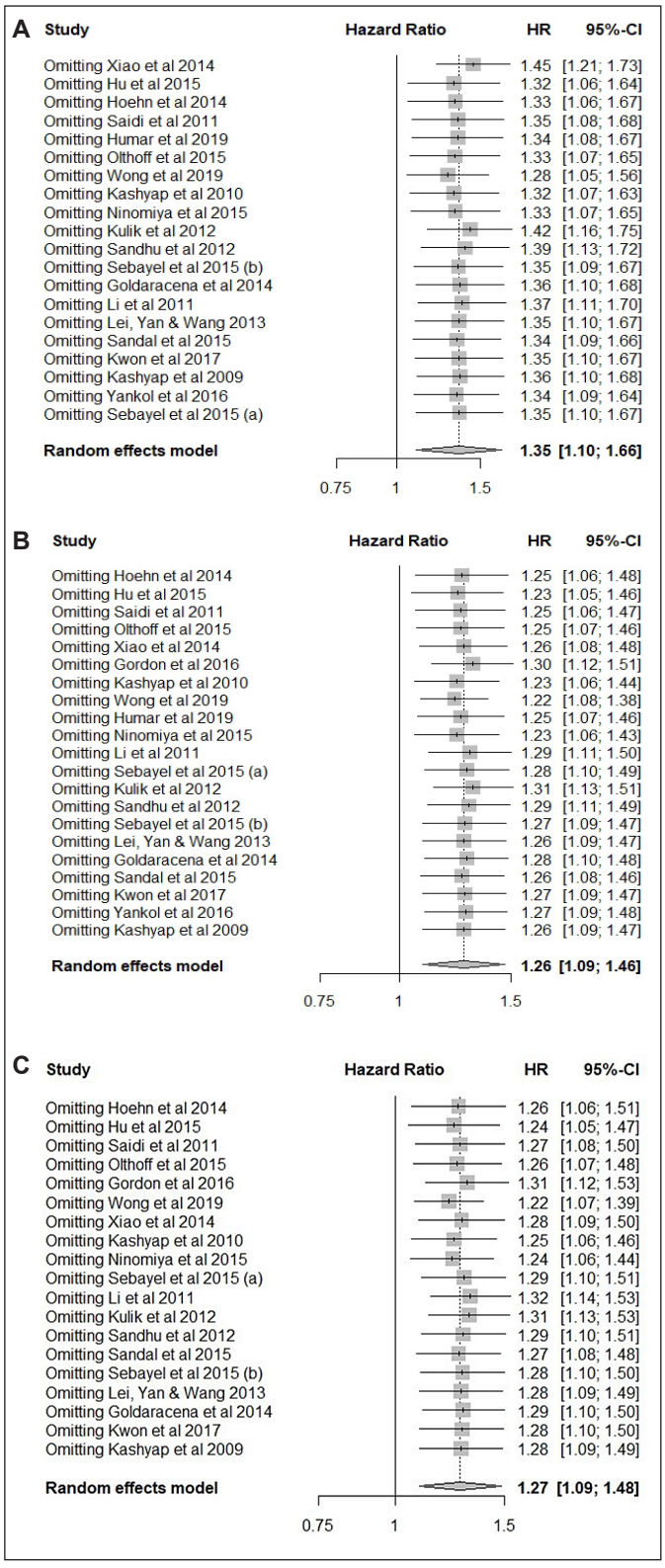

FIGURE 4. Survival analysis of patients undergoing liver transplantation with deceased or living donors, using the leave-one-out method: a) 1-year survival, b) 3-year survival and c) 5-year survival. DDLT: deceased donor liver transplant; LDLT: living donor liver transplant.

Wong et al.[4] did not explain the heterogeneity found (1% and 15%, respectively) as well as did not change the data either, maintaining favorable results for LDLT (1.24 HR, 95%CI 1.04–1.47, I^2=71.2%, *P*=0.0117 and 1.22 HR, 95%CI 1.08–1.38, I^2=56.9%, *P*=0.0022).

We assessed asymmetries by visually inspecting the funnel plots of patient survival at 1, 3, and 5 years of follow-up. However, we did not confirm any asymmetry by the statistical tests of Egger and Begg[12,13].

Regarding the subgroup analysis, we identified an improved patient survival with statistical significance for individuals over 50 years of age in favor of the LDLT group at intervals of 3 and 5 years with, respectively, 1.23 HR (1.04–1.44, I^2=33%, *P*=0.01) and 1.22 HR (1.01–1.48, I^2=58%, *P*=0.04) (TABLE 1).

TABLE 1. Survival analysis considering a subgroup of patients with an age cut-off.

Subgroup (age)	k	Hazard ratios	CI95%	I^2	Weight	*P*
Patient survival at 1 year						
<50	4	1.08	0.68–1.71	72%	31.3%	0.73
≥50	12	1.26	0.95–1.66	68%	68.7%	0.11
Patient survival at 3 years						
<50	4	1.15	0.89–1.49	55%	33.9%	0.29
≥50	12	1.23	1.04–1.44	33%	66.1%	0.01
Patient survival at 5 years						
<50	4	1.18	0.99–1.39	34%	32.6%	0.06
≥50	11	1.22	1.01–1.48	58%	67.4%	0.04

Graft survival

Nine studies were meta-analyzed for graft survival at 1 and 3 years[15,16,19,20,25,28-31], and seven for 5-year survival[15,19,20,25,28,30,31]. Overall, our meta-analysis evaluated 21,276 grafts, 85% of which correspond to the DDLT group. When assessing the HR individual distribution in the Forrest plot, only the studies by Hoehn et al.[31] and Kashyap et al.[20] showed statistical significance in favor of LDLT in the first year. On the other hand, the study from Hoehn et al.[31] was the only one that found statistically significant results, which favored the DDLT group in the fifth year (FIGURE 5.A and 5.C).

The grouped analyzes showed low heterogeneity for survival at 1 and 3 years (I^2=0% and 34% respectively), and high heterogeneity for 5 years (I^2=78%). In the overall analysis, the 1-year survival evaluation showed a statistically significant difference between the groups, favoring the LDLT group (1.36 HR, 95%CI 1.16–1.60, *P*<0.0001), while the 3-year survival (1.13 HR, 95%CI 0.96–1.33, *P*<0.13), and 5 (0.99 HR, 95%CI 0.74–1.33, *P*<0.96), did not differ significantly.

Baujat's graphical analysis (FIGURE 6) identified the study from Hoehn et al.[31] as the main contributor to heterogeneity in 3 and 5 years. The leave-one-out method (FIGURE 7) assessed the impact on the results after removal from the study of Hoehn et al.[31]. It found a statistically significant effect in favor of LDLT in 3 years (1.24 HR; 95%CI 1.08–1.4, I^2=0%, *P*=0.0023), while follow-up at one year there were no differences among groups. At 5-year analysis it was detected a non-statistically significant increase in the effect [1.12 HR (95%CI 0.97–1.28, I^2=0%, *P*=0.11)].

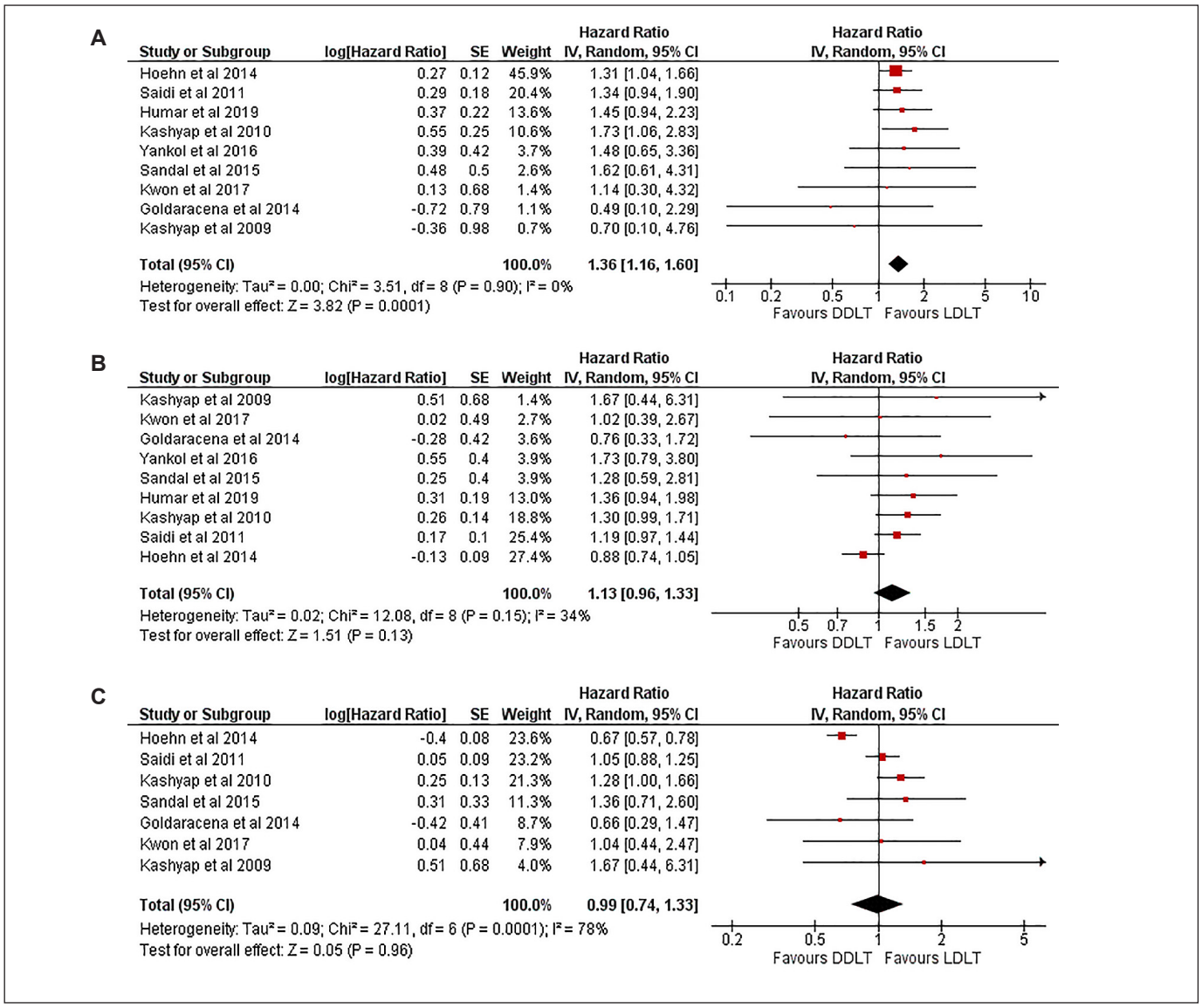

FIGURE 5. Survival of the liver graft considering the type of living or deceased donor: a) survival at 1 year, b) survival at 3 years and c) survival at 5 years.

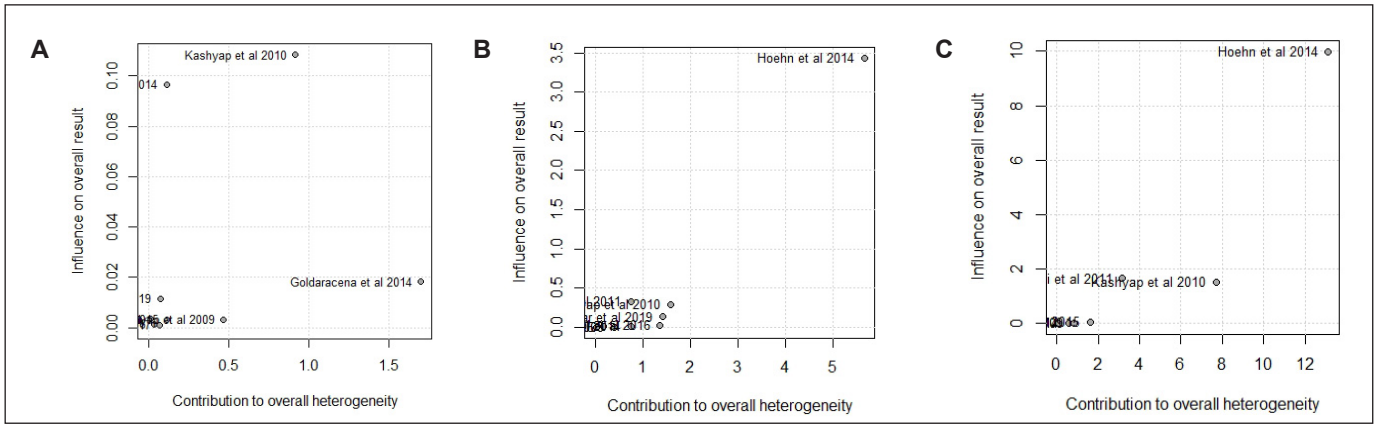

FIGURE 6. Analysis of heterogeneity using the Baujat graph, assessing graft survival in patients undergoing liver transplantation: a) 1 year survival, b) 3-year survival and c) 5-year survival.

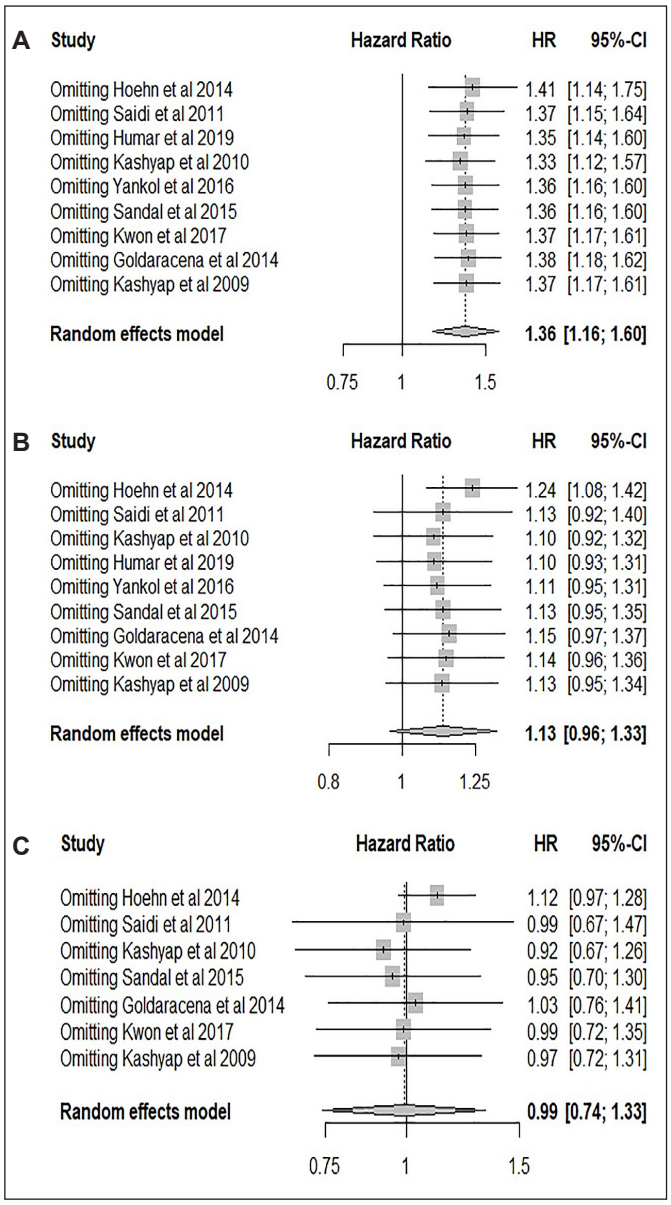

FIGURE 7. Survival analysis of grafts from patients undergoing liver transplantation with a deceased or living donor, using the leave-one-out method: a) 1-year survival, b) 3-year survival and c) 5-year survival.

In the subgroup analysis, we found a significant HR effect of 1.31 (1.08–1.59, I^2=0%, *P*=0.007) in favor of the LDLT group for individuals 50 years old at one-year follow-up (TABLE 2).

TABLE 2. Survival analysis of graft considering a subgroup of patients with an age cut-off.

Subgroup (age)	k	Hazard ratios	CI95%	I^2	Weight	*P*
Graft survival at 1 year						
<50	3	1.31	1.08–1.59	0%	91.5%	0.007
≥50	3	1.15	0.61–2.18	0%	8.5%	0.66
Graft survival at 3 years						
<50	3	1.04	0.79–1.36	64%	82.8%	0.80
≥50	3	1.13	0.68–1.86	5%	17.2%	0.64
Graft survival at 5 years						
<50	3	0.89	0.58–1.35	87%	77.1%	0.57
≥50	2	0.81	0.45–1.46	74%	22.9%	0.49

DISCUSSION

Many authors have explored several strategies to improve the number of donors without compromising the recipient results. Thus, it is necessary to know and compare the outcomes of living and deceased donor liver transplantation, including the ideal technique, results, and ethics. In this study, we meta-analyzed studies that evaluated an overall large number of patients undergoing liver transplantation, assessing the patient and the graft survival according to the type of donor, living or deceased (N=32,258 for survival analysis and N=21,276 for graft analysis).

Liver transplantation with a graft from a deceased donor is the most performed, but the supply is lower than the demand. Our meta-analysis detected a better survival at 1, 3, and 5 years in adult liver transplant patients who received an LDLT graft. When considering individuals over 50 years old, patients undergoing LDLT also had better survival results. The analysis of graft survival varied according to adjustments performed, showing better 1-year survival for LDLT recipients when compared to DDLT, including receivers older than 50 years. The 5-year graft survival was similar among groups.

Literature data differ in terms of survival analysis considering the different types of donors in liver transplantation. Kashyap et al.[20] evaluated patients with chronic autoimmune liver disease (autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis). Similarly, to our study, they observed a better patient survival for LDLT, being the patient survival at 1, 3, and 5 years, respectively, of 95.5%, 93.6%, and 92.5% for LDLT, and 90.9%, 86.5%, and 84.9% for DDLT (*P*=0.002). The graft survival at 1, 3 and 5 years was 87.9%, 85.4% and 84.3% for LDLT and 85.9%, 80.3% and 78.6% for DDLT (*P*=0.123). On the other hand, Hoehn et al.[31] evaluated 14,282 patients undergoing DDLT and 715 patients undergoing LDLT and found no differences in survival rates over the years (patient survival at 1, 3 and 5 years were, respectively: DDLT – 90.1 %, 80% and 72.6% and LDLT – 90.1%, 84.1% and 78.6%; graft survival at 1, 3 and 5 years: DDLT – 90%, 80% and 78% and LDLT -85%, 78% and 70%). In Hoehn's analysis, individuals submitted to LDLT had a greater chance of readmission 30 days after discharge (rate of 44% vs 37.1%; *P*=0.001).

Gavriilidis et al.[6] also performed a systematic review and network meta-analysis on survival following right lobe split graft, living- and deceased-donor liver transplantation in adult patients[6]. A pairwise meta-analysis demonstrated that there were no significant differences in graft and patient survival outcomes. Bayesian network meta-analysis showed no significant differences in 1, 3, and 5-year graft and patient survival between the three alternative liver transplantations. Such differences, found in both the results of patient and graft survival, may be associated with the sample size since the authors included fewer studies in their review. For the analysis of graft survival, the meta-analysis by Gavriilidis et al.[6] included six studies referring to the follow-up of 1, 3, and 5 years while the present analysis has used data from eight studies for the

follow-up of 1 and 3 years, and seven studies for the follow-up of 5 years. Regarding patient survival, Gavriilidis et al.[6] evaluated eight studies for the follow-up of 1, 3, and 5 years, while we obtained twice as many studies.

In another meta-analysis that evaluated controlled studies, Wan P et al.[32] compared LDLT and DDLT outcomes. The authors included 19 studies totaling 5,450 patients. They analyzed five postoperative complications: biliary and vascular, intraabdominal bleeding, perioperative death, and re-transplantation. They also evaluated the following four perioperative outcomes: duration of the recipient operation, red blood cell transfusion requirement, length of the hospital stay, and cold ischemia time.

The study found no significant difference in the perioperative mortality between LDLT and DDLT recipients. On the other hand, LDLT had a higher rate of surgical complications after transplantation. However, it is interesting to mention that the authors reported their data using the odds ratio, which considers only the number of events and not the time in which they have occurred, being less appropriate to analyze the results from time to time, according to Tierney et al.[33]. In our review, we used HR, suggested as the most appropriate method to analyze survival.

The results of previous studies, including earlier metanalysis, associated with the results of our own reinforce the usefulness of utilizing living donor living livers and reassurance that patient and graft survival are the same as or greater for LDLT compared to DDLT[34-36].

This meta-analysis used the process of searching and selecting articles by two independent researchers. It also followed the Prism Declaration, an internationally recognized guideline. It utilized the Newcastle-Ottawa Scale to assess the risk of bias of each included article. The outcomes of interest were analyzed using HR, considering the temporal influence on them. This meta-analysis may have some limitations. Our study could have suffered the influence of publication bias or language bias. Data from "grey literature" has not been evaluated. Moreover, part of the results was analyzed using HR, which may overestimate or underestimate the variable effect.

In conclusion, we observed better patient survival at 1, 3, and 5 years among patients who received living donor liver transplantation (LDLT), compared to DDLT, as well as better 1-year graft survival. Thus, the present study provides further support to maintain the indications for living donor liver transplantation when appropriate since it is a viable option with acceptable patient and graft survival rates.

Authors' contribution

Cavalcante LN participated in the project design, selection, and review of articles, as well as writing of the scientific article. Queiroz RMT performed search and selection of articles, review of eligibility criteria and writing. Paz CLSL performed the statistical analysis of the data. Lyra AC contributed to the discussion and final review of the manuscript.

Orcid

Lourianne Nascimento Cavalcante: 0000-0003-1110-0931.
Renato Macedo Teixeira de Queiroz: 0000-0002-9811-1598.
Cláudio Luiz da S L Paz: 0000-0002-9766-7324.
André Castro Lyra: 0000-0001-9010-8645.

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RESUMO – Contexto – O transplante de fígado com doador falecido é a primeira escolha, mas o transplante de doador vivo é uma alternativa a ser considerada em situações especiais, como falta de órgãos doados e emergências. Até o momento, não há consenso sobre qual método de transplante proporciona melhor sobrevida e menos complicações, sendo, ainda, um ponto em aberto para discussão. **Métodos –** Esta meta-análise comparou as taxas de sobrevida de pacientes e enxertos de 1, 3 e 5 anos de transplante de doador vivo e transplante de fígado com doador falecido. Incluímos estudos publicados de abril de 2009 a junho de 2021 e adotamos o modelo genérico do inverso da variância para o efeito aleatório das razões de risco. A adequação dos estudos foi determinada por meio da Escala de Newcastle-Ottawa – NOS (WELLS). **Resultados –** Para análise de sobrevida do paciente, incluímos um total de 32.258 indivíduos. Encontramos uma melhor sobrevida estatisticamente significativa para o grupo de transplante de fígado de doador vivo em 1, 3 e 5 anos, respectivamente: 1,35 HR (IC95% 1,10–1,66, *P*=0,005), 1,26 HR (IC95% 1,09–1,46, *P*=0,002) e 1,27 HR (IC95% 1,09–1,48, *P*=0,002). Nossa meta-análise avaliou um total de 21.276 enxertos. Na análise geral, a sobrevida em 1 ano foi melhorada em favor do grupo de transplante de doador vivo (1,36 HR, IC95% 1,16–1,60, *P*<0,0001), enquanto a sobrevida em 3 anos (1,13 HR, IC95% 0,96–1,33, *P*<0,13) e 5 (0,99 HR, IC95% 0,74–1,33, *P*<0,96), não diferiram significativamente. **Conclusão –** Esta meta-análise detectou uma sobrevida estatisticamente significativa maior do paciente em 1, 3 e 5 anos favorecendo o transplante de doador vivo em comparação com o transplante de fígado com doador falecido, bem como uma diferença estatisticamente significativa melhor na sobrevida do enxerto em 1 ano favorecendo o grupo de transplante de doador vivo.

Palavras-chave – Transplante de fígado; transplante de fígado de doadores vivos; transplante de fígado de doador falecido.

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