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Review Article

Changes of long-term survival of resection and liver transplantation in hepatocellular carcinoma throughout the years: A meta-analysis

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A R T I C L E I N F O

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A B S T R A C T

Background: Hepatocellular Carcinoma (HCC) still is one of the most detrimental malignant diseases in the world. As two curative surgical therapies exist, the discussion whether to opt for liver resection (LR) or transplantation (LT) is ongoing, especially as novel techniques to improve outcome have emerged for both. The aim of the study was to investigate how the utilization and outcome of the respective modalities changed through time.
Methods: We searched Medline and PubMed for relevant publications comparing LT and LR in HCC patients during the time period from 1990 to 2022, prior to March 31, 2023. A total of 63 studies involving 19,804 patients – of whom 8178 patients received a liver graft and 11,626 underwent partial hepatectomy - were included in this meta-analysis.
Results: LT is associated with significantly better 5-year overall survival (OS) (64.83%) and recurrence-free survival (RFS) (70.20%) than LR (OS: 50.83%, OR: 1.79, $p < 0.001$; RFS: 34.46%, OR: 5.32, $p < 0.001$). However, these differences are not as evident in short-term intervals. Older cohorts showed comparable disparities between the outcome of the respective modalities, as did newer cohorts after 2005. This might be due to the similar improvement in survival rates that were observed for both, LT (15–23%) and LR (12–20%) during the last 30 years.
Conclusion: LT still outperforms LR in the therapy of HCC in terms of long-term survival rates. Yet, LR outcome has remarkably improved which is of major importance in reference to the well-known limitations that occur in LT.

1. Introduction

Hepatocellular Carcinoma (HCC) positions sixth concerning frequency and causes around 782.000 deaths yearly [1]. This makes it the fourth-deadliest cancer on the planet. Curative treatment comprises of liver resection (LR) and liver transplantation (LT) [1]. By its nature LT in general is more radical and resects the liver cirrhosis which is the precancerosis for HCC [2]. LR is widely available, has hardly any waiting time, and can achieve comparable results to LT [2]. Additionally, patients have no need for life-long immunosuppression after the operation [3]. It is however limited by the future liver remnant (FLR) and its functional capacity after resection, and is concomitant with a quicker recurrence in the remaining cirrhotic liver [4,5].

In the last 30 years, both resection and liver transplantation have undergone substantial developments [6]. The introduction of the MILAN-Criteria and other restrictions to HCC transplantation, improved intra- and perioperative management, and modern immunosuppression was able to optimize the results achieved with LT [3,7]. Better allocation

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schemes, the introduction of standard exception MELD (Model of End-stage Liver Disease) and now increasing focus on tumor biology compared to a mere description of the morphology of the tumors have further increased LT results to 5-year overall survival (OS) of above 80% [7–13]. Concomitantly, LR has also evolved strongly. The identification of resectable patients has been markedly improved by CT and MRI volumetry and dynamic tests for liver function e.g. Maximum liver function capacity (LiMAx) [6]. Additionally, resection techniques allow for more precise resection with less blood loss [14]. Also, perioperative management has improved to prevent complications, which have a negative influence on long-term survival [15]. In recent years the use of minimally invasive surgery has also shown its potential for improved results [16–18].

Since there is a large overlap in patients who could benefit from either resection or transplantation and the fact that livers suitable for transplantation remain scarce numerous studies, both experimental and observational, have tried to triangulate the perfect allocation between LT and LR [19–24]. Also, meta-analyses have attempted to create meaningful subgroups of studies to identify groups of patients who do not necessarily need an LT. Recently, it has been suggested that the advances in LT and LR have a relevant influence on the results between both interventions [6].

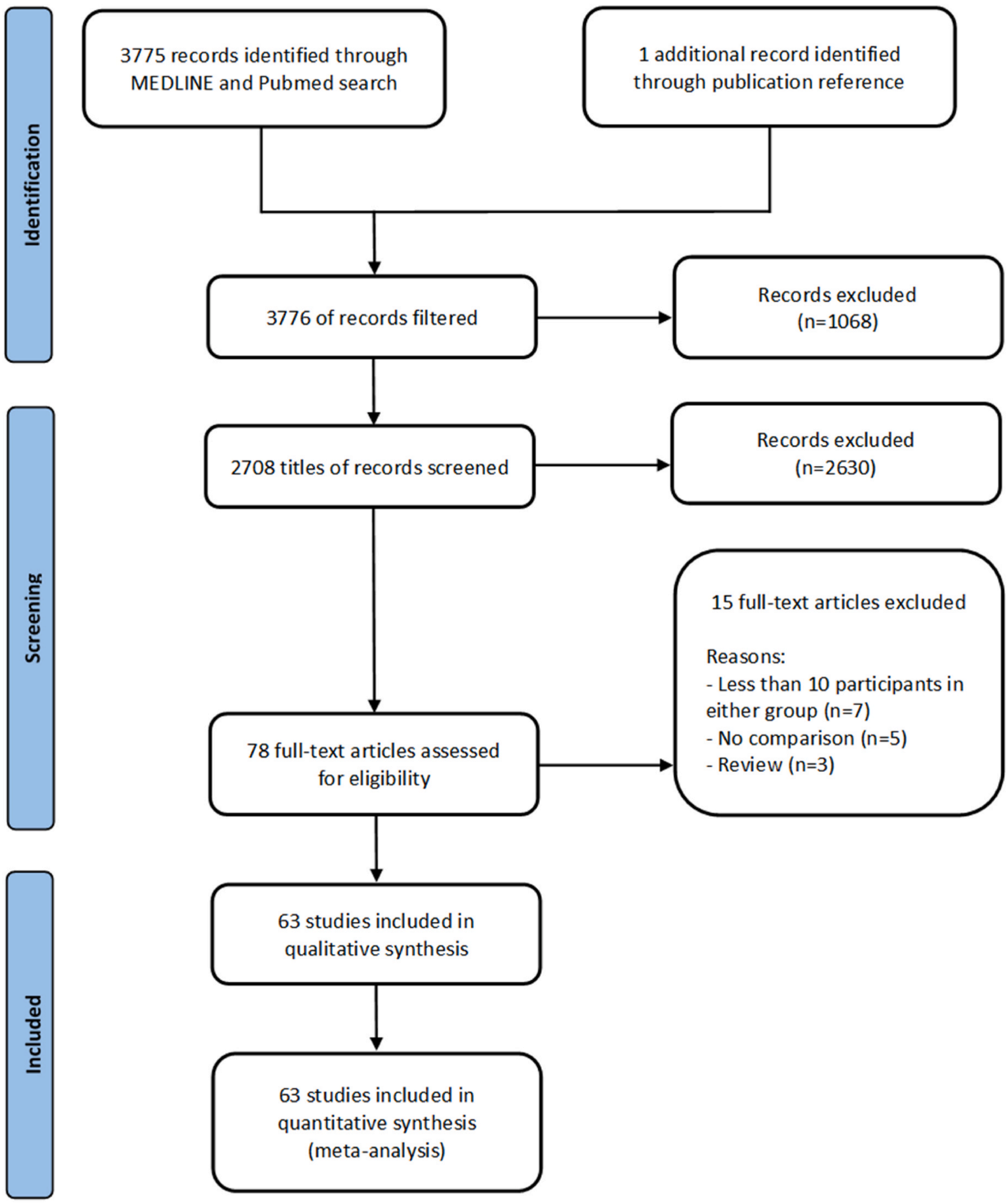

Fig. 1. Flow diagram describing the pathway from initial literature research towards final meta-analysis for HCC patients being treated either with liver resection or transplantation.

This study was designed to investigate the changes in OS obtained with either LR or LT through time. Furthermore, we assess how OS has developed based on the study period. In addition, as secondary outcomes, RFS, morbidity, and mortality for LR and LT were analyzed and compared.

2. Materials and methods

2.1. Registration of this study

This meta-analysis was registered with the International Registry of Systematic Reviews (PROSPERO, Centre for Reviews and Dissemination, University of York) under the ID CRD42023396762 and was performed as per the PRISMA proclamation [25].

2.2. Search strategy and study selection

We scanned Medline and PubMed for significant publications. The search terms were chosen broad to include as many publications as possible: “hepatocellular carcinoma”, “resection” and “transplantation”. Then, we used the Filter: “Clinical Research”, “Clinical Research”, “Comparative Research”, “Datasets”, “Journal Articles”, “Meta-Analysis”, “Multicenter Studies”, “Observational Studies”, “Reviews”, and “Systematic Reviews”. Initially our search was restricted to the period 1990 to June 2022 (Fig. 1). The leftover articles were checked against exclusion criteria: non-human, articles not accessible in English, and case reports were rejected. Studies with an observation time of under 1 year or with under 10 patients were prohibited. Studies were finally checked and extracted data was moved to the RevMan (RevMan, adaptation 5.4.0; Copenhagen, Nordic Cochrane Center, Cochrane Collection, 2008) application for additional investigation. The last date each database was consulted was the 31st of March 2023.

Because of significant changes in the evaluation, operative treatment and perioperative treatment of patients receiving liver resection and liver transplantation we chose to divide the studies by the time period investigated in the studies. We deliberately chose the time period investigated by the studies to divide up the publications, since the scientific process often results in a several-year-long lag until final acceptance and publication. To allow for analysis via scatterplot we chose the middle year of investigation. As previously described, the year 2005 might be as close as possible to a watershed moment in which many changes confluenced that changed the results of both LR and LT [6]. These changes not only comprise the incremental utilization of liver function testing before LR, but first and foremost reflect the implementation of MELD score based allocation for LT. Therefore, this year was defined as the threshold. Studies investigating cohorts within time periods that contain both, years before and after 2005, might be confounded to originate heterogeneous data. Therefore, these studies were excluded from the calculation of OR and the Forest plot to receive a clearer picture of the available data.

Baseline information that was extracted included study type, sample size, sex, age, duration of follow-up, and Child-Turcotte-Pugh (CTP) score. MBS and MD confirmed the results. Incongruent results were discussed amongst MBS and MD and settled agreeably.

2.3. Quality assessment

The RevMan Risk-of-Bias instrument and funnel plots were utilized to find and characterize biases. Patient blinding (execution and identification bias) couldn’t be evaluated as this was not possible in review studies.

2.4. Statistical analysis

Continuous factors are introduced utilizing median with 95% confidence interval. We investigated all included studies. Additionally, we divided the analysis into subgroups of studies either investigating patients before or after 2005. All treatment comparisons are calculated as Odds Ratio (OR) with 95% confidence interval, applying the Mantel-Haenszel test. A random-effects meta-analysis was performed, and heterogeneity was evaluated utilizing I^2. Chi-square test, Fisher’s exact tests and U-tests were utilized when appropriate and $p < 0.05$ was used to convey significance. Additionally, 5-year OS and RFS were investigated through time with correlation analysis, calculating coefficient of determination R^2. Test for overall effect is conveyed by Z-value. OS was the primary endpoint. RFS, complications, and early mortality were regarded as secondary endpoints.

3. Results

3.1. Study inclusion

N = 3775 studies were found in the literature search conducted using Medline and PubMed. There were 2708 studies left after filtering. Altogether, 78 full-texts were evaluated, and 63 studies totaling 19,804 patients were eventually included in the study (Fig. 1) [4,6,23,26–85]. The research involved 8178 liver transplant recipients and 11,626 patients who had partial hepatectomy. Table 1 presents the baseline information for each study that is included. In accordance to previous studies, LR cohorts comprised patients with an elevated median age (+3.8 years; p = 0.001) in with decreased rate of relevant liver insufficiency as expressed by the CHILD-Pugh-Score (CHILD C −14.2%; p < 0.001), as compared to LT cohorts (Table 1).

3.2. Study quality

It had to be assumed that there was a substantial danger of selection bias and inaccurate reporting because all the studies were retrospective. In general, funnel plots were symmetrical. Additionally, some individual studies revealed the following biases: liver transplants from live donors, methods not stated, patients received some form of neoadjuvant therapy, modifications to the list of indications and contraindications, liver transplants for recurrence after liver resection, varying follow-up times for comparison groups, examination of patients with tumor thrombi, and

Table 1
Description of baseline characteristics and demographic data from all 63 studies evaluating liver resection and transplantation for HCC included in the meta-analysis. CI: Confidence Interval; HCC: Hepatocellular Carcinoma; LR: liver resection; LT: liver transplantation; mo: months; y; years.

Baseline demographic data from all included studies	All, N (%)/Median [95% CI]	HCC Treatment Modality		p-Value (LR vs. LT)
		-Resection (LR)-N (%)/Median [95% CI]	*-Transplantation (LT)*-N (%)/Median [95% CI]	
Number of patients				
	19,804 (100%)	11,626 (58.7%)	8178 (41.3%)	–
Sex				0.46
Male	14,129 (77.7%)	8487 (77.5%)	5642 (78.0%)	
Female	4048 (22.3%)	2458 (22.5%)	1590 (22.0%)	
Age (y)				
	57.0 [56.0–59.0]	59.5 [58.0–60.5]	55.7 [54.6–57.0]	**0.001**
Length of follow-up (mo)				
	38.3 [32.5–42.7]	36.0 [30.0–42.7]	39.3 [32.4–48.1]	0.77
CHILD-Pugh Score				**<0.001**
A	5341 (66.8%)	4223 (84.9%)	1118 (37.0%)	
B	2136 (26.7%)	697 (14.0%)	1439 (47.7%)	
C	515 (6.4%)	53 (1.1%)	462 (15.3%)	

one study of incidentalomas. Assessment of study biases is displayed in Supplemental Fig. 3.

Throughout the meta-analyses, heterogeneity remained substantial. Also, after partition into subgroups heterogeneity generally remained over 50%.

3.3. Survival

3.3.1. All studies

For the majority of trials, 1-, 3-, and 5-year survival statistics were provided. LR and LT initially showed themselves to have the same 1-year OS rates in the analysis of all studies (LR 8195/9458 [86.27%] versus LT 5222/6207 [84.13%]; OR: 0.98 [0.82, 1.17]; p = 0.82) (Suppl. Fig. 1A), which was not statistically significant. At 3-years after surgery the meta-analysis showed considerably better outcomes after liver transplantation than after liver resection (LR 5159/7772 [66.38%] versus LT 3658/5229 [69.96%]; OR 1.31 [1.10, 1.57]; p = 0.003) (Suppl. Fig. 1B). LT considerably outperformed LR at 5-years of follow-up (LR 3571/7025 [50.83%] versus LT 3586/5531 [64.83%]; OR: 1.79 [1.48, 2.15], p < 0.001) (Suppl. Fig. 1C).

RFS differences were more pronounced. From year 1 on LT showed a significant improvement of RFS compared to LR (Suppl. Figs. 2A–C). This gap widened considerably during the 5 years of follow-up. The results are listed in Supplemental Table 1.

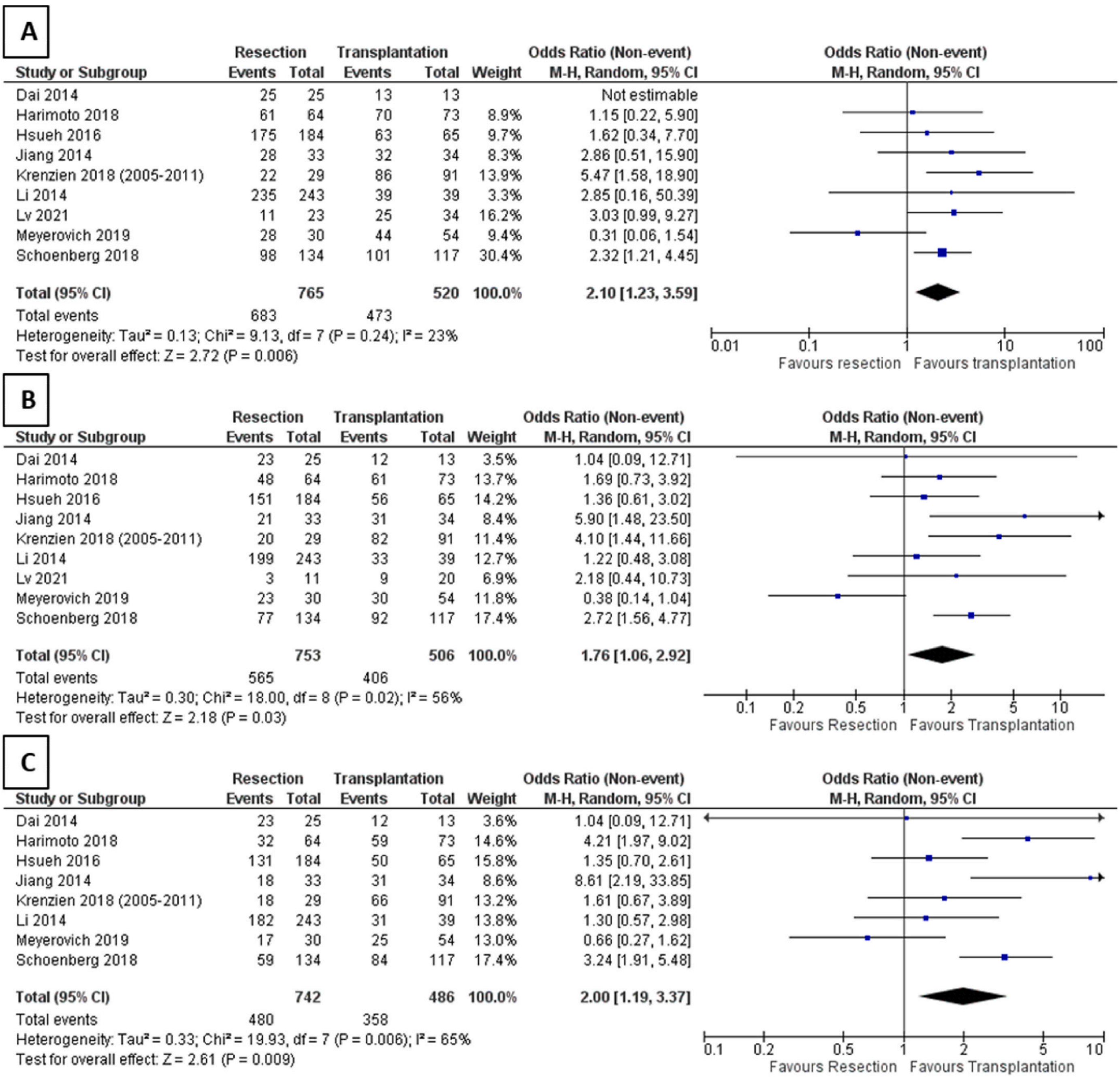

Fig. 2. Forest plots of overall survival (OS) in HCC patients, stratified for comparison between liver resection and liver transplantation, investigated in cohorts after 2005. Results displayed for OS at 1-year follow-up (A), at 3-years follow-up (B) and at 5-years follow-up. CI: Confidence interval; M–H: Mantel-Haenszel test; random: Random effect.

3.3.2. Investigation time-period until 2005

25 studies reported on patients treated before 2005. There was no significant difference to the results observed in all studies. At 1-year LR and LT were on par (LR 1567/1944 [80.61%]; LT 1277/1675 [76.24%]; OR: 0.83 [0.63, 1,09]; p = 0.18). At 3-years LT and LR results did not show any statistically significant difference (LR 1073/1776 [60.42%]; LT 931/1522 [61.17%]; OR: 1.08 [0.83, 1.42]; p = 0.56). After 5-years LT significantly outperformed LR (LR 689/1517 [45.42%]; LT 722/1310 [55.11%]; OR: 1.56 [1.14, 2.15]; p = 0.006).

RFS differences were the same as with all studies. From year 1 until year 5 LT significantly outperformed LR. The results are listed in Supplemental Table 1.

3.3.3. Investigation time-period after 2005

9 studies reported outcomes that were obtained after 2005. Similar to the previously reported outcomes at 1-year, LR and LT almost had the same results in terms of overall survival with a slight beneficial tendency towards LT (LR 683/765 [89.28%]; LT 473/520 [90.96%]) However, this difference was already statistically significant (OR: 2.10 [1.23, 3.59]; p = 0.006) (Fig. 2A). At 3- and 5- years, LT and LR also showed statistically significant differences that were evident in terms of survival proportions (3-years: LR 565/753 [75.03%]; LT 406/506 [80.24%]; OR: 1.76 [1.06, 2.92]; p = 0.03) (5-years: LR 480/742 [64.69%]; LT 358/486 [73.66%]; OR: 2.00 [1.19, 3.37]; p = 0.009) (Fig. 2B and C).

As previously reported RFS remained significantly better after LT than LR (Fig. 3A–C). The results are listed in Supplemental Table 1.

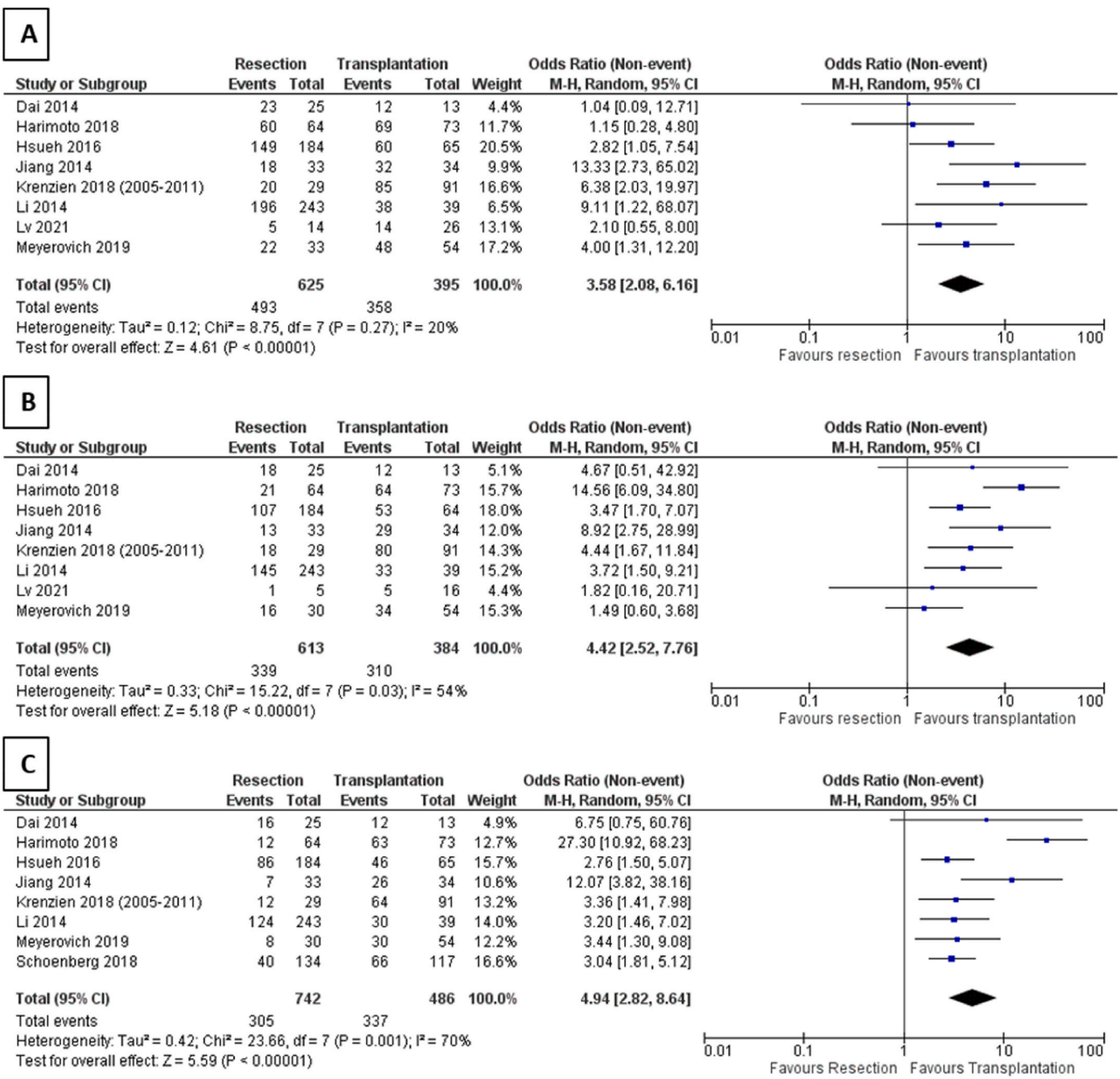

Fig. 3. Forest plots of disease-free survival (DFS) in HCC patients, stratified for comparison between liver resection and liver transplantation, investigated in cohorts after 2005. Results displayed for DFS at 1-year follow-up (A), at 3-years follow-up (B) and at 5-years follow-up. CI: Confidence interval; M–H: Mantel-Haenszel test; random: Random effect.

3.4. Correlation of investigation time-period and survival

In order to investigate how the results after LR and LT have changed over time, we performed a correlation analysis over a time period of 30 years in which the observation was obtained. OS after LR steadily increased through time (LR: $R^2 = 0.166$; LT: $R^2 = 0.455$). On average LR improved about 12–20% (Fig. 4A), RFS only increased by about 7%. LT also improved strongly over the years. On average, LT increased OS by 15–23% (Fig. 4B), RFS only improved by about 2–4% (Supplemental Table 1).

4. Discussion

Regarding curative liver resection and transplant in HCC, this meta-analysis offers an update of the relevant literature. Subgroup analysis was also carried out to demonstrate the changes in the management of HCC patients over time. In opposition to the literature, the research clearly shows that liver resection and liver transplant are still not equivalent [6]. Patients with poor liver function should receive a transplant as their liver function is restored. Despite having more complications than resection, transplant increases patients' chances of 5-year survival [19]. In contrast, only individuals with adequate liver function should have their livers resected [19,48]. These patients don't have to wait long for curative care and are not dependent of life-long immunosuppressant therapy following surgery [61].

In this study, we mostly could not show any change in relative differences between LR and LT over time. In the group of studies conducted before 2005 3 years after operation the difference of LR and LT did not reach statistical significance. This is in contrast to previously published research [6]. The changes measured in previous work might be due to local changes in treatment and treatment quality. Inspired by these results we additionally conducted a correlation analysis through time. However, especially regarding long-term follow-up studies conducted before 2005 and after 2005 show that LT remains the gold standard for curative HCC treatment.

The fact that the gap between LR and LT might have even widened does not mean that there has not been any improvement in the surgical management of HCC. In fact, constant innovation has resulted in a remarkable increase in OS over the years [6,17]. As described above LR could improve by about 20% and LT could even improve by up to 25% in

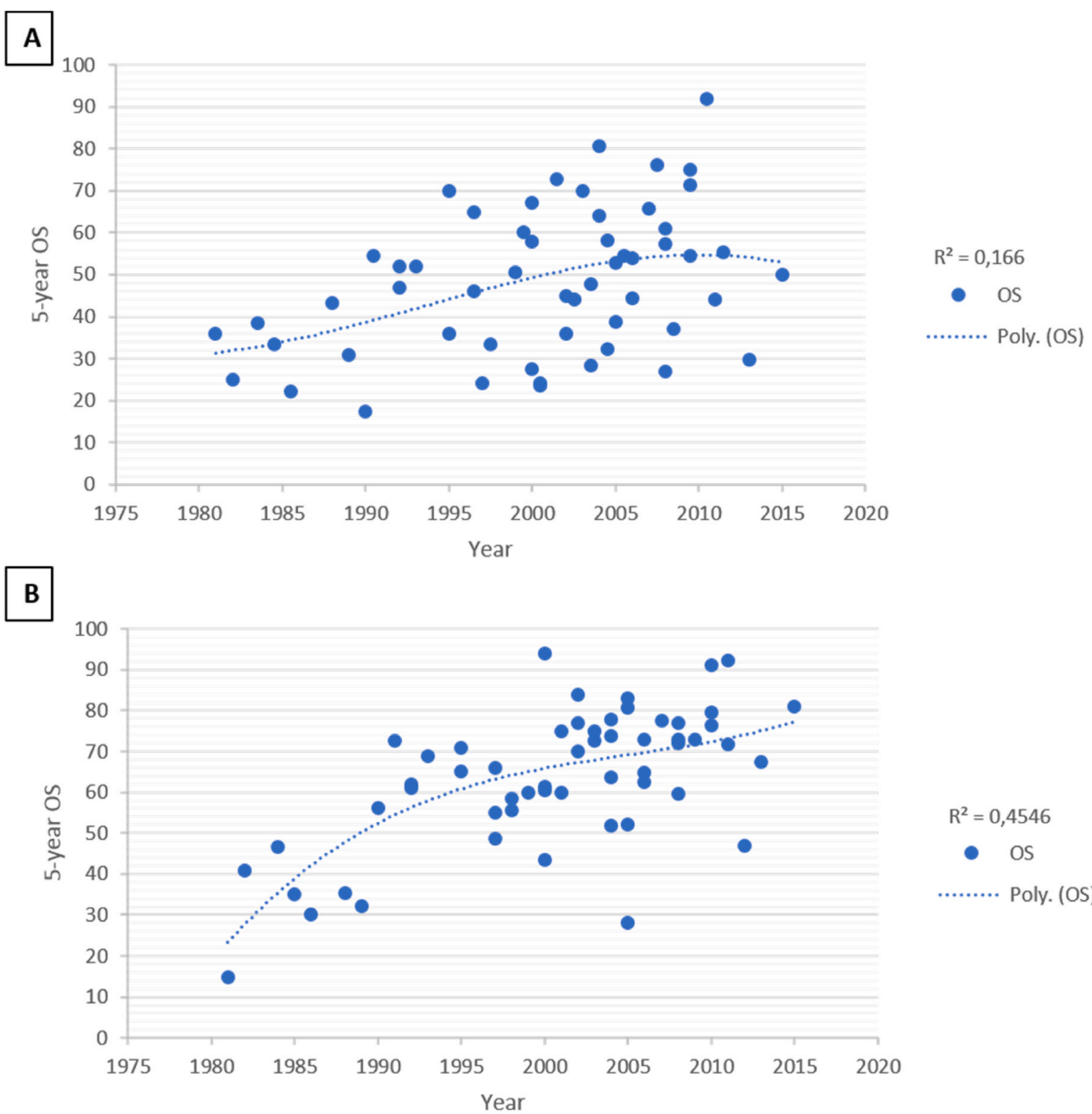

Fig. 4. Correlation Analysis of research time period and 5-year-OS after LR (A) and LT (B). OS: Overall Survival; R2: coefficient of determination.

ca. 30 years. On one hand, this can be attributed to improvements in the operative techniques [17,86]. On the other, both surgeons and anesthesiologists alike have learned to improve their respective perioperative patient management [87]. A better understanding of pharmacokinetics in patients with liver disease has a noticeable impact [87,88]. The use of selective dissection methods allows for more FLR and makes the need for a Pringle maneuver unnecessary in many cases [89]. This reduces blood loss and the rate of liver failure postoperatively [89]. Also, postoperative treatment has improved markedly in recent years. The stronger improvement of results after LT might have contributed to the fact that now the risk difference between LR and LT reached statistical significance at 3 years of follow-up.

Interestingly, in our analysis the rate of RFS stayed steadier over time. Combined with the increase in OS, this indicates that management of recurrence has also improved significantly [90–92]. The armamentarium of treatments ranges from vastly improved systemic treatment (e.g. Checkpoint Inhibitors) and interventional techniques (e.g. radiofrequency ablation and brachytherapy) to rescue liver grafts [90–92]. Additionally, salvage liver transplantation is a well-established option since most patients suffering from recurrence still are transplantable [4]. The lack of an improvement in RFS however indicates that there needs to be an improved prediction of whom might develop recurrence. According to published data, patients who were stratified based on their liver's biology – as described by the respective degree of cirrhosis – and tumor's immunology may attain almost the same 5-year OS and vastly improved RFS rates following liver resection [19]. Also, Artificial Intelligence might help to identify patients at risk for relapse. These patients should be considered for LT or at least monitored more closely [20]. This also points towards the need for adjuvant treatment, especially in LR patients. For instance, adjuvant chemotherapy improved recurrence free survival in colorectal cancer patients by 5%, leading to 3-year RFS of up to 78.2% [93]. HCC patients with cirrhosis are vulnerable to conventional chemotherapy and therefore not suitable. These patients could greatly benefit from e.g. immune-modulatory systemic treatment that takes the decreased liver function into account [94].

The results of this study are the product of a thorough evaluation and meta-analysis of literature. Given that all of the evaluated research was retrospective, there are structural issues with the included articles. Currently, prospective comparison studies are not possible, most likely for ethical and practical reasons (number of suitable patients). Retrospective studies of all patients revealed a substantial level of heterogeneity. We found no evidence of publication bias in our funnel plots.

However, a relevant height of the risk for selection bias needs to be pointed out (Supplemental Fig. 3). This represents a limitation that almost any retrospective meta-analysis needs to deal with and must be considered when interpreting the respective results [95]. In our case, the selection bias is maintained by the fact that the majority of outcome results of the included studies derive from therapy-specific cohorts – after the respective therapy has been performed. In contrast, an exact number of patients who dropped out of the chosen therapy sequence prior to performing the actual surgery is not consequently given – which is especially relevant for the LT cohort [27,28,85]. Removal from the waiting list, i.e. due to tumor progression in HCC patients, is a well-known problem in transplant medicine and leads to drop-out of the intended therapeutic strategy, hereby exceeding the LR drop-out rate by approximately 10-fold in small HCCs [26,27]. Therefore, a profound intention-to-treat analysis which could provide even more thorough insights on whether to opt for LT or LR for specific patients cannot be performed on basis of these data. This lack of knowledge impairs the comparability between the two therapeutic strategies. Among the few publications that provide a profound intention-to-treat analysis by including pre-treatment drop-outs, Adam et al. were still able to show significantly better OS for LT in contrast to LR [27].

The subgroup analysis attempted to investigate the changes over time. The year 2005 was chosen based on the results of a well-published report and on historical observation [6]. The respective authors describe the implementation of the MELD score in 2006 as the pivotal tool to change LT allocation practice and thus its results. Furthermore, relevant changes in preoperative functional liver tests predicting the outcome of the future liver remnant are associated with a more elaborate patient selection for LR and have influenced the therapeutic sequence from then on. Because studies examining the results from LR and LT are conducted continuously, we had to exclude several studies since they investigated patients from both before and after 2005. This might have introduced a bias in the results.

In conclusion, this study could show that LT remains the gold standard for curative treatment of HCC as it is associated with favorable long-term overall survival. The relative differences in OS and DFS between LR and LT have barely changed over time. However, this is due to a parallel improvement in results for both treatment options. RFS has changed only minimally over time which is especially relevant for LR. Future research should concentrate on improving RFS after liver resection to reduce the number of HCC patients on the LT waiting list and therefore decrease the pressure on the donor pool in general.

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Data availability statement

The data used in this meta-analysis derive from publicly available studies and can be accessed as defined in the reference section. Other review-specific data including the protocol are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Moritz Drefs: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft, Visualization. **Markus B. Schoenberg:** Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft, Visualization. **Nikolaus Börner:** Conceptualization, Investigation, Data curation, Formal analysis, Visualization, Writing – review & editing. **Dionysios Koliogiannis:** Conceptualization, Investigation, Data curation, Writing – review & editing. **Dominik T. Koch:** Conceptualization, Investigation, Visualization, Writing – review & editing. **Malte J. Schirren:** Conceptualization, Investigation, Writing – review & editing. **Joachim Andrassy:** Methodology, Validation, Writing – review & editing. **Alexandr V. Bazhin:** Methodology, Validation, Resources, Writing – review & editing, Project administration. **Jens Werner:** Methodology, Validation, Resources, Writing – review & editing, Project administration. **Markus O. Guba:** Conceptualization, Methodology, Validation, Resources, Formal analysis, Writing – original draft, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare no competing interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2024.107952.

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