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SYSTEMATIC REVIEW

Long-term posttransplant survival outcome following bridging locoregional therapy in hepatocellular carcinoma patients: A systematic review and meta-analysis

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Key words
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Abstract

Aim: Liver transplantation (LT) is essential due to its curative efficacy, but liver-graft shortages have limited its widespread application. Bridging locoregional therapy (LRT) before LT has been performed to prevent tumor progression, and a recent literature review revealed that it is associated with a nonsignificant trend toward better survival outcomes. However, much more information on bridging therapy has become available since then. This meta-analysis aimed to compare the posttransplant survival and HCC recurrence between patients with and without pretransplant bridging LRT.
Methods: Studies were identified in MEDLINE, SCOPUS, and the Cochrane Library. Two independent researchers screened titles and full articles, extracted relevant data, and conducted a parametric survival analysis.
Results: Out of 4794 studies, 18 cohort studies were eligible. The 1-, 3-, and 5-year overall survival (OS) rates were 93.1%, 85.0%, and 79.1% for those in the bridging LRT group, while they were 91.8%, 81.1%, and 75.5% for those who did not receive LRT, respectively. There were no differences in overall survival between these groups (HR 0.90; 0.78–1.05, P = 0.17). Interestingly, we discovered that bridging therapy helped prolong survival significantly in a high-risk population with a long waiting time (HR 0.76; 0.60–0.96, P = 0.02). Unfortunately, bridging LRT did not improve disease-free survival (HR 0.98; 0.86–1.11, P = 0.70).
Conclusions: The results indicate that bridging LRT does not generally change post-LT outcomes. However, bridging LRT can significantly improve survival in patients with a long waiting time for LT.

Introduction

Hepatocellular carcinoma (HCC) is a primary liver cancer and is responsible for nearly 800 000 deaths worldwide. Currently, it is the fourth most common cause of overall cancer-related death.[1] Despite various novel therapeutic interventions, there have not been any substantial changes in the curative treatment algorithm. Liver transplantation (LT) has been considered one of the most effective treatments for HCC. Typically, LT is performed on decompensated cirrhotic patients with early-stage HCC. The tumors must fulfill Milan criteria: one lesion ≤5 cm or three lesions all <3 cm without evidence of extra-hepatic spread or vascular invasion.[2] However, the availability of liver-donor grafts is insufficient relative to demand, leading to drop-out from the waiting list due to tumor progression beyond the transplant eligibility period.

Pretransplant bridging locoregional therapy (LRT), also known as bridging therapy, has emerged over the last two decades to delay tumor progression while waiting for a liver donor. The guidelines endorsed by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) support bridging therapy for patients who are waiting for LT who have Organ Procurement and Transplant Network (OPTN) T2 staging or fulfill the Milan criteria. However, this support is based on limited data from observational studies.[3,4] Despite the advantage of LRT for disease progression control, it could also increase worsening liver function and precipitate complications associated with clinically significant portal hypertension.

Some non-randomized controlled trials have evaluated the treatment effects of bridging LRT. However, the synthesized evidence showed no significant difference in posttransplant 5-year overall survival (OS) and disease-free survival (DFS) outcomes, and the risk ratios were determined as 0.88 (0.76–1.01) and 0.92

(0.75–1.13), respectively.[5] The reasons for these findings could be a low number of studies (i.e., three to five) and a small number of patients (242 to 324) included in the synthesis for both outcomes.

Since then, a few non-RCT studies have been published.[6–8] An intention-to-treat (ITT) review study based on a small population (255 to 267) revealed a different outcome with significant improvement in survival outcomes after LT at 1, 3, and 5 years. Even though the results showed a beneficial effect of the treatment using ITT analysis, the report included only studies with ITT analysis, and several studies needed to be included. The analysis did not include some factors regarding serum alpha-fetoprotein (AFP), tumor burden, or wait time.

Therefore, we performed an updated systematic review and meta-analysis to estimate and compare OS and DFS between HCC patients with and without bridging LRT. We aimed to fill the gap in various clinical aspects, including tumor size, waiting time, serum AFP levels, and the expertise of performing centers. Subgroup analyses were done to contribute to precision treatment suited for a heterogeneous spectrum of patients.

Methods

We conducted this meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Supplement 1) and registered it at PROSPERO (CRD42021270236). A comprehensive systematic search was conducted on MEDLINE via PubMed, SCOPUS, and Cochrane Library databases from the inception date to January 10th, 2024. The search was carried out using the following search terms: "hepatocellular carcinoma" or "HCC" AND "liver transplant" AND "Milan criteria" AND "bridging therapy" or "locoregional therapy" or "LRT" or "transarterial embolization" or "TACE" or "TARE" or "microwave ablation" or "MWA" or "radiofrequency ablation" or "RFA" or "ethanol injection" or "PEI" or "stereotactic body radiation therapy" or "SBRT" AND "survival" or "recurrent" or "drop-out" (Supplement 2). We also searched for additional references in the included manuscripts. Figure 1 illustrates the literature search process in a PRISMA flowchart. References of excluded studies are available upon request.

Selection of studies. Two independent reviewers (A.C. and A.S.) determined the eligibility of each article by inspecting titles and abstracts. If the eligibility was equivocal, we extracted full articles for complete review. A third investigator (A.T.) resolved any disagreements. Studies were eligible if they met all of the following criteria: (i) study population: unresectable HCC with staging compliant with Milan criteria; (ii) intervention: any listed LRT whether alone or combined, including trans-arterial chemoembolization (TACE), microwave ablation (MWA), radiofrequency ablation (RFA), trans-arterial radioembolization (TARE), ethanol injection (EI), or stereotactic body radiation therapy (SBRT); (iii) comparison: direct comparison of LT with LRT and without LRT; (iv) outcome measures: endpoints including overall survival (OS), disease-free survival (DFS), or non-dropping out survival rates; (v) study design: cohort studies.

We excluded studies if they met any of the following criteria: (i) The study was a case–control study, case report, conference abstract, review, expert opinion, or editorial comments. (ii) LT was performed on candidates whose HCC staging did not satisfy the Milan criteria at the time of transplantation. (iii) The study had insufficient data. (iv) The study was a duplicate or a part of another included study. (v) The study had a sample size of less than 10 cases. (vi) The study had a follow-up time of less than 1 year.

Data extraction and quality assessment. Two reviewers (A.C. and A.S.) extracted the following essential parameters from the included studies: (i) the first author and publication year, country or region of the studied population, and study design; (ii) sample size, patients at risk in both groups at 1, 3, or 5 years, patient baseline demographics including mean ages and sex, tumor characteristics including mean tumor size and numbers, baseline serum AFP level, bridging locoregional therapy protocols, transplant waiting time; and the (iii) OS, DFS, drop-out rate, and hazard ratio and 95% confidence interval (CI) of each. Information not mentioned in the original manuscripts was requested from the corresponding authors.

To calculate hazard ratios (HRs) for each time interval, we used a curve approach with the WebPlot Graph Digitizer program version 4.4. The probabilities and times of OS and DFS were extracted from the published Kaplan–Meier curves and the reported numbers of at-risk patients. Then, we constructed time-to-event data at the individual level using STATA's ipdfc command. Two reviewers (A.C. and A.S.) used the Risk of Bias In Non-randomized Studies of Interventions (ROBIN-I tool)[23] to assess the quality of the cohort studies. Any disagreements were resolved by consensus with a third reviewer (A.T.).

Outcome of interest. There were two outcomes of interest: OS and DFS. OS refers to the length of time starting from the transplant date to death or the date of the last follow-up visit. DFS refers to the length of time measured from the transplant date until the HCC recurrence date, including intra- and extra-hepatic locations. Disease progression was defined as an increase in the number or size of viable tumors from those that initially comply with the Milan criteria to beyond the criteria despite the bridging LRT.[7]

Statistical analysis and data synthesis. A mixed-effect Weibull survival regression was applied to estimate the treatment effect on OS and DFS based on simulated individual time-to-event patient data. We also performed subgroup analyses for OS according to AFP levels, LT waiting time, type of LRT, and tumor size. The heterogeneity between studies was evaluated using the I^2 statistic. The publication bias was assessed through a funnel plot, Egger's test, and a contour-enhanced funnel plot. All analyses were performed with STATA version 17.0 (Stata Corporation, College Station, Texas, USA). A P-value less than 0.05 was considered statistically significant.

Results

Study selection and quality assessment. We identified 4794 studies from the search databases and seven records from manual search. We removed 441 duplicated studies, and after reviewing titles and abstracts, we excluded 4340 irrelevant

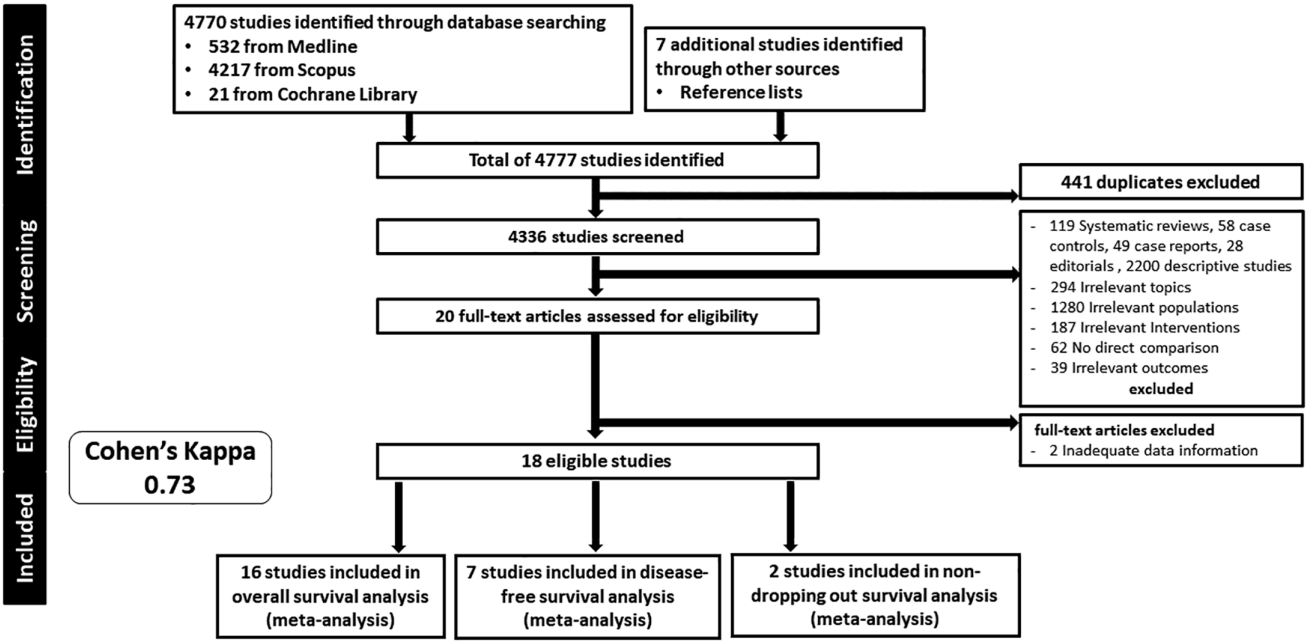

Figure 1 PRISMA flowchart outlining literature search.[6–22]

studies for several reasons (see Fig. 1). After excluding these studies, 20 full-text articles were evaluated. Two studies were excluded due to data insufficiency, even upon further inquiry. Eighteen non-RCT studies were eligible and included in this meta-analysis.[6–22,24] The kappa agreement between the two reviewers was 0.73, indicating substantial agreement.

Of the 18 studies,[6–22,24] 4170 patients received bridging LRT, and 2599 did not. Information on the OS, DFS, and non-drop-out rates was available in 16,[6–13,15–20,22,24] seven,[7,9,10,13,18,19,21] and two[13,14] studies, respectively. The baseline characteristics of studies and patients are described in Table 1. The majority of the included patients were 50 to 60 years old and had one or two tumors in which the largest diameter was 2–3 cm. Most of them received liver grafts from deceased donors. Only two studies from South Korea and one study from Japan included patients receiving living donor liver transplantation predominantly. Most patients underwent LT after bridging therapy with TACE as the dominant modality. However, the waiting time and serum AFP levels varied between studies.

All included single-center studies had fewer than 50 transplant cases per year for HCC patients, which are considered low transplant volume.[25] Only three studies[6,7,21] reached a mean annual volume of more than 50 cases per year, but they were all multicenter studies. None of the patients had received systemic treatment or immune checkpoint inhibitors as neoadjuvant or adjuvant treatment. According to the ROBIN-I assessment, there were only low to moderate risks of biases among these studies (Table 2).

Overall survival. Individual patient data were simulated for 16 studies,[6–13,15–20,22,24] which provided the 1-, 3-, and 5-year OS rates or KM curves for the groups with and without bridging LRT. The pooled 1-, 3-, and 5-year OS rates of those with bridging LRT therapy were 93.1%, 85.0%, and 79.1%, respectively. The corresponding OS probabilities in patients without bridging LRT were 91.8%, 81.1%, and 75.5%, respectively. We applied a parametric survival analysis (Weibull model) to estimate the HRs comparing OS between two groups. The pooled HR was 0.90 (95% CI: 0.78–1.05; $P = 0.17$), which demonstrated that the OS between the groups was not significantly different (Fig. 2). There was a slightly longer but not statistically significant median survival time in the bridging LRT group compared with the no-LRT group (17.2 *vs* 15.3 years).

Disease-free survival. Individual patient data were simulated for 7 studies,[7,9,10,13,18,19,21] which provided the 1-, 3-, and 5-year DFS rates or KM curves for the groups with and without bridging LRT. The pooled 1-, 3-, and 5-year DFS survival rates for patients in the bridging LRT group were 92.4%, 81.8%, and 73.1%, while the corresponding probabilities for patients without bridging therapy were 89.0%, 79.6%, and 73.0%, respectively. The HRs were estimated and pooled across studies, yielding a pooled HR of 0.98 (95% CI: 0.86–1.11; $P = 0.70$) (Fig. 3). This result demonstrated no difference in DFS between the two groups.

Non-drop-out survival rates. An analysis of two studies[13,14] indicated 6- and 12-month non-drop-out survival rates of 94.26% and 88.70% in the bridging LRT group, respectively. The corresponding possibilities in the non-bridging LRT group were 89.29% and 80.16%, respectively. The pooled HR was 0.86 (95% CI: 0.46–1.59; $P = 0.63$), which showed that bridging therapy did not change the non-drop-out survival.

Table 1 Characteristics of the included studies

Author (Year), Country	Study design	Type of OLT LRT [%LDLT/ % DDLT]//no LRT [%LDLT/ % DDLT] (Overall)	Bridging protocol (Mena number of LRT)	Population number (n) Total (LRT/no LRT)	Mean age (year) LRT/no LRT	MELD score at transplant LRT/no LRT	Tumor mean size (cm) LRT/ no LRT	Wait time (months) LRT/no LRT	Initial AFP level (ng/ml) LRT/no LRT	Conclusion
Kim.[9] Korea	Retrospective cohort	[78.8/22.2]// [90.5/9.5]	TACE (NA)	57 (36/21)	49/52	19/22	2.5/2.8	NA	198/1012	No different in OS and DFS
Porrett.[10] US	Retrospective cohort	[0/100]//[0/100]	TACE19%, RFA 45%, combined 36% (NA)	64 (31/33)	52/56	12.1/14.7	3.1/2.4	1.8/3.9	NA	No different in OS and DFS
Eguchi.[11] Japan	Retrospective cohort	[100/0]//[100/0]	TACE 50%, PEI 28%, RFA 22%(2)	29 (18/11)	57/NA	NA	1.8/NA	NA/11	30.3/NA	No different in OS
Lao[12] US	Retrospective cohort	[0/100]//[0/100]	RFA 67%, TACE 13%, PEI 16%, and combined 4% (NA)	124 (33/91)	54/55	11.7/12.1	3.7/2.6	14.4/11.4	229/225	LRT was associated with improved DFS.
Dubay.[13] Canada	Retrospective cohort	[11.8/88.2]// [14.585.5]	RFA (1.1)	127 (51/76)	55/56	14/15	2.4/2.5	9.5/5.0	28/20	No different in OS and DFS
Frangakis.[14] US	Retrospective cohort	[0/100]//[0/100]	TACE (NA)	65 (22/43)	57/53	21/20	3/2	6.8/7.0	2301/350	TACE decreased drop-off risk.
Heinzow.[15] Germany	Retrospective cohort	[0/100]//[0/100]	TACE (1.9)	28 (17/11)	60/58	NA	NA	5.4/6.8	1151/60 000	No different in OS and DFS
Cabrera.[16] US	Retrospective cohort	[0/100]//[0/100]	PEI (NA)	80 (33/47)	NA	NA	NA	1.8/5.4	NA	No different in OS and DFS
Eswaran.[17] US	Retrospective cohort	[0/100]//[0/100]	TACE (NA)	35 (28/7)	56/60	12/11	3.8/4.0	10.2/3.1	240/9	No different in OS
Seehofer.[18] Germany	Retrospective cohort	[0/100]//[0/100]	TACE (NA)	117 (38/79)	NA	NA	NA	6.2/3.7	NA	LRT was associated with improved DFS.
Sourianarayana.[19] US	Retrospective cohort	[0/100]//[0/100]	TACE 62%, RFA 30%, and others 8% (NA)	225 (93/132)	58/57	12/16	NA	2.9/3.3	NA	No different in OS and DFS
Kim.[20] US	Retrospective cohort	[0/100]//[0/100]	TACE 63%, RFA 13%, and combined 24% (NA)	173 (112/61)	NA	NA	NA	NA	NA	LRT was associated with improved DFS.

(*Continues*)

Table 1 (Continued)

Author (Year), Country	Study design	Type of OLT LRT [%LDLT/ % DDLT]//no LRT [%LDLT/ % DDLT] (Overall)	Bridging protocol (Mena number of LRT)	Population number (n) Total (LRT/no LRT)	Mean age (year) LRT/no LRT	MELD score at transplant LRT/no LRT	Tumor mean size (cm) LRT/ no LRT	Wait time (months) LRT/no LRT	Initial AFP level (ng/ml) LRT/no LRT	Conclusion
Agopian.[21] US	Retrospective cohort	[0/100]//[0/100]	TACE 53.3%, RFA 13.0%, Combined 8.3%, Others 4.7% (1)	3601 (2854/747)	59/56	12/17	2.5/2.3	NA	21/15	No different in OS and DFS
Al Sebayel.[22] Saudi Arabia	Retrospective cohort	(45.2/54.8)	TACE, TARE, RFA (NA)	111 (30/81)	NA	NA	NA	> 3/>3	NA	No different in OS
Xing.[8] US	Retrospective cohort	[0/100]//[0/100]	TACE 72%, RFA 16%, and others 12% (NA)	205 (111/94)	55/58	16/15	2.4/2.3	6/11	N/A	LRT was associated with improved OS.
Habibollahi.[24] US	Retrospective cohort	[0/100]//[0/100]	TACE 75.5%, RFA 13.5%, Combined 9% and others 2%	287 (155/132)	56.1/56.5	10.4/12.5	3.7/3.2	4.4/1.8	NA	No different in OS.
Lee.[7] Korea	Retrospective cohort	(92.5/7.5)	TACE 59%, RFA 7%, Combined 31%, and others 3%	473 (123/350)	53.8	NA	NA	9	10.9	No different in OS and DFS
Wallace.[6] UK	Retrospective cohort	[0/100]//[0/100]	TACE	968 (385/583)	49.2/48.2	NA	NA	5.2/3.3	86/88	No different in OS.

AFP, alpha-fetoprotein; DDLT, disease donor liver transplantation; LDLT, living donor liver transplantation; LT, liver transplantation; NA; non-applicable; OLT, orthotopic liver transplantation; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transarterial-chemoembolization.

Table 2 Quality of included studies evaluated by the ROBIN-I tool

Author (Year)	Confounding	Selection of participants	Classification of Intervention	Deviations of intended interventions	Missing data	Measurement of outcomes	Selection of reported results	Overall risk of bias
Kim.[9]	Low	Low	Low	Low	Moderate	Low	Low	Moderate
Porrett.[10]	Moderate	Low	Moderate	Low	Moderate	Low	Low	Moderate
Eguchi.[11]	Low	Low	Moderate	Low	Moderate	Low	Low	Moderate
Lao.[12]	Low	Low	Moderate	Low	Moderate	Low	Low	Moderate
Dubay.[13]	Low	Low	Low	Low	Low	Low	Low	Low
Frangakis.[14]	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Heinzow.[15]	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Cabrera.[16]	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Eswaran.[17]	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Seehofer.[18]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Sourianarayana.[19]	Moderate	Low	Moderate	Low	Moderate	Low	Low	Moderate
Kim.[20]	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Agopian.[21]	Moderate	Low	Moderate	Low	Moderate	Low	Low	Moderate
Al Sebayel.[22]	Low	Low	Moderate	Low	Moderate	Low	Low	Moderate
Xing.[8]	Moderate	Low	Moderate	Low	Moderate	Low	Low	Moderate
Habibollahi.[24]	Low	Low	Moderate	Low	Low	Low	Low	Moderate
Lee.[7]	Low	Low	Moderate	Low	Moderate	Low	Low	Moderate
Wallace.[6]	Low	Low	Low	Low	Moderate	Low	Low	Moderate

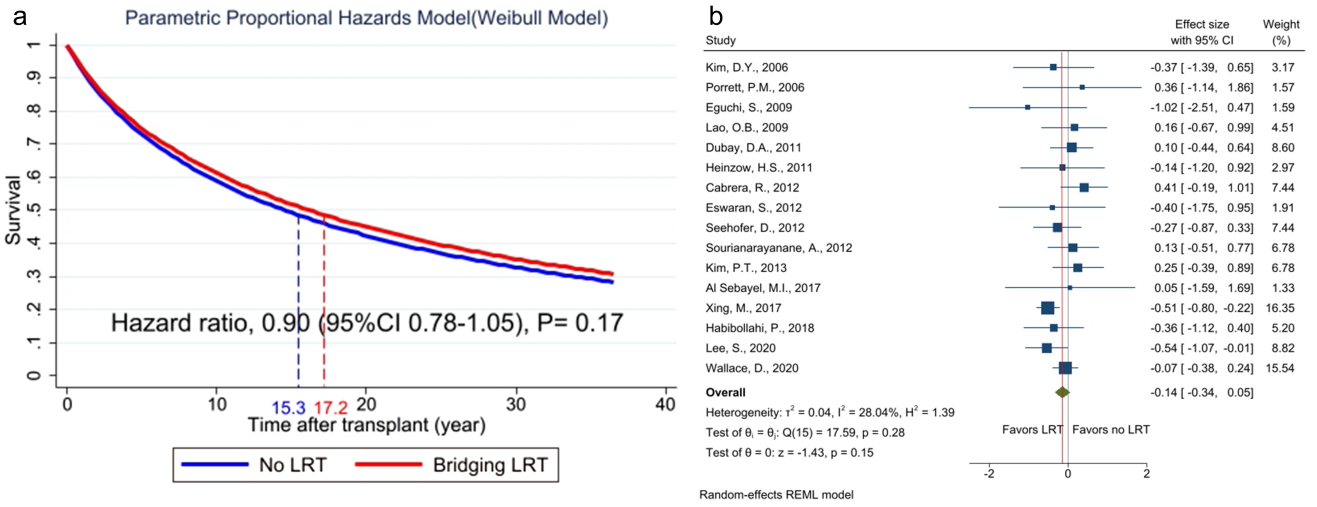

Figure 2 The survival function of overall survival estimated by the Weibull model (a) and forest plot (b).

Subgroups analysis. We investigated the effect of bridging LRT on various specific subgroups to see which types of patients would benefit most from the treatment. We also evaluated patients who were on the transplant list for long periods (6 months or more) and short periods (3 months or less).[26] Notably, the survival analysis of seven studies[7,8,10,12,13,17,18] showed statistically significant improvement in OS in the bridging LRT group compared with the no-LRT group (HR = 0.76, 95% CI 0.60–0.96, $P = 0.02$) (Fig. 4). On the other hand, there was no significant difference in OS between patients receiving bridging LRT and those who did not receive it in the short-term waitlist subgroup (HR 1.15, 95% CI 0.75–1.77, $P = 0.52$). There is a non-statistically significant improvement the OS in the studies in Asian countries that predominately performed LDLT (HR 0.54, 95% CI 0.42–0.69, $P = 0.32$),[7,9,11,22] in contrast to studies from North America (HR 0.99, 95% CI 0.84–1.21, $P = 0.94$)[8,10,12,13,16,17,19,20,24] or European (HR 0.89, 95% CI 0.68–1.18, $P = 0.43$) counties[6,15,18] that predominantly performed DDLT. Also, LRT in Asian countries' populations has not improved the DFS. (HR 1.01, 95% CI 0.57–1.78, $P = 0.98$).[7,9]

Regarding the AFP levels, bridging LRT did not affect OS in either the patients with normal or mildly elevated serum AFP (AFP <100 ng/mL; HR = 1.00, 95% CI 0.79–1.27, $P = 0.99$)[6,11,13,20] or patients with markedly elevated serum AFP (AFP ≥100 ng/mL; HR = 0.93, 95% CI 0.55–1.56,

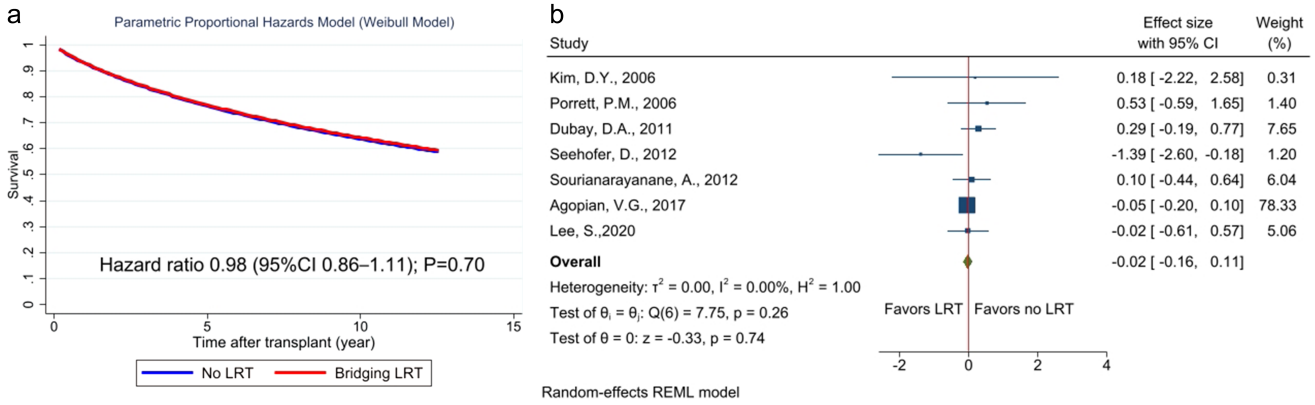

Figure 3 The survival function of disease-free survival estimated by the Weibull model (a) and forest plot (b).

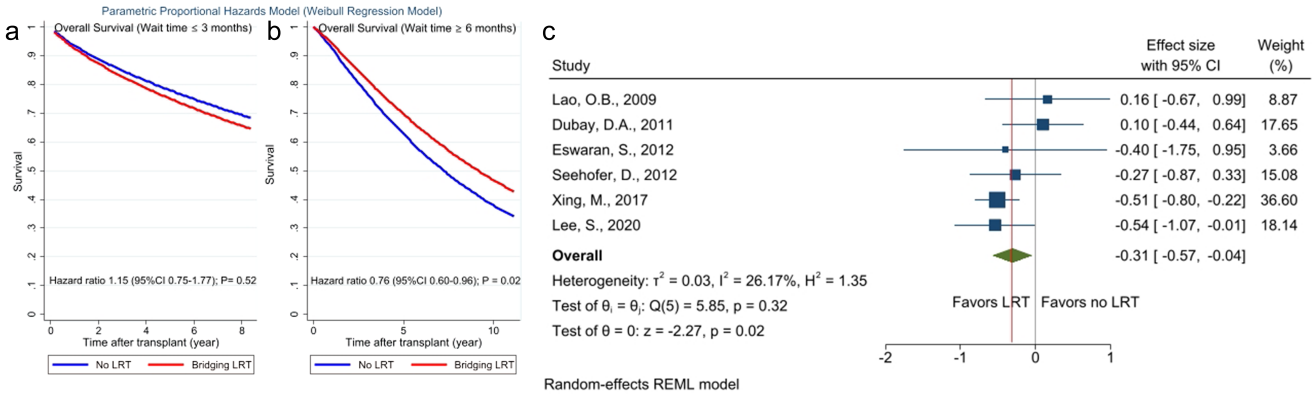

Figure 4 Survival function of the short-waiting-time population estimated by the Weibull model (a) and long-waiting-time population estimated by the Weibull model (b) and forest plot (c).

$P = 0.77$).[15,18,21,24] Likewise, the bridging LRT did not alter the OS (HR = 0.75, 95% 0.36–1.58, $P = 0.46$) and DFS (HR = 1.18, 95% CI 0.11–13.04, $P = 0.89$) outcomes in the patient with extremely high levels of serum AFP (AFP ≥500 ng/mL).[9,15] In terms of nodules number, LRT did not cause a significant impact on OS (HR = 1.11, 95% CI 0.80–1.53, $P = 0.53$) and DFS (HR = 1.00, 95% CI 0.89–1.12, $P = 0.95$) in the patients with one or two nodules.[9,13,19,20] Bridging LRT before LT did not improve the survival outcomes in patients with an extensive tumor with a mean size larger than 3 cm (HR 0.85, 95% CI 0.54–1.33, $P = 0.47$).[12,17,18] Also, there was no distinct advantage from a specific type of pretransplant therapy according to the results from studies using TACE treatment alone (HR 0.86, 95% CI 0.67–1.11),[6,9,15,17,18] RFA alone (HR 1.10, 95% CI 0.64–1.88, $P = 0.75$), or PEI alone (HR 1.51, 95% CI 0.83–2.76, $P = 0.18$).

Heterogeneity and publication bias. There was a low level of heterogeneity in OS and no heterogeneity in DFS analyses, and the I^2 values were 28.0% and 0%, respectively (Figs 2, 3). However, there was considerable heterogeneity in the non-drop-out survival analysis, for which the I^2 value was 77.4%. Publication bias was evaluated using a funnel plot and Egger's test. There was asymmetry in the funnel plot of OS analysis. However, further investigation was done using a contour-enhanced funnel plot and Egger's test, which yielded a result of 0.53 (SE = 0.38, $P = 0.19$), demonstrating no significant publication bias. The cause of the asymmetry is likely due to heterogeneity rather than publication bias.

The funnel plot of the DFS analysis seemed symmetrical, suggesting no significant publication bias. Egger's test value was −0.12 (SE = 2.07, $P = 0.96$) for DFS, which confirmed this finding (Fig. 5). A subgroup analysis of the long-term waitlist population showed an acceptable degree of heterogeneity ($I^2 = 0.24$).

Discussion

This systematic review and meta-analysis included the most recent studies from various regions over the past two decades. We meticulously devised a methodology to select studies, which yielded 16,[6–13,15–20,22,24] seven,[7,9,10,13,18,19,21] and two[13,14] cohort studies comparing OS, DFS, and non-drop-out survival between patients with and without bridging LRT, respectively. We also conducted subgroup analyses and estimated the median time

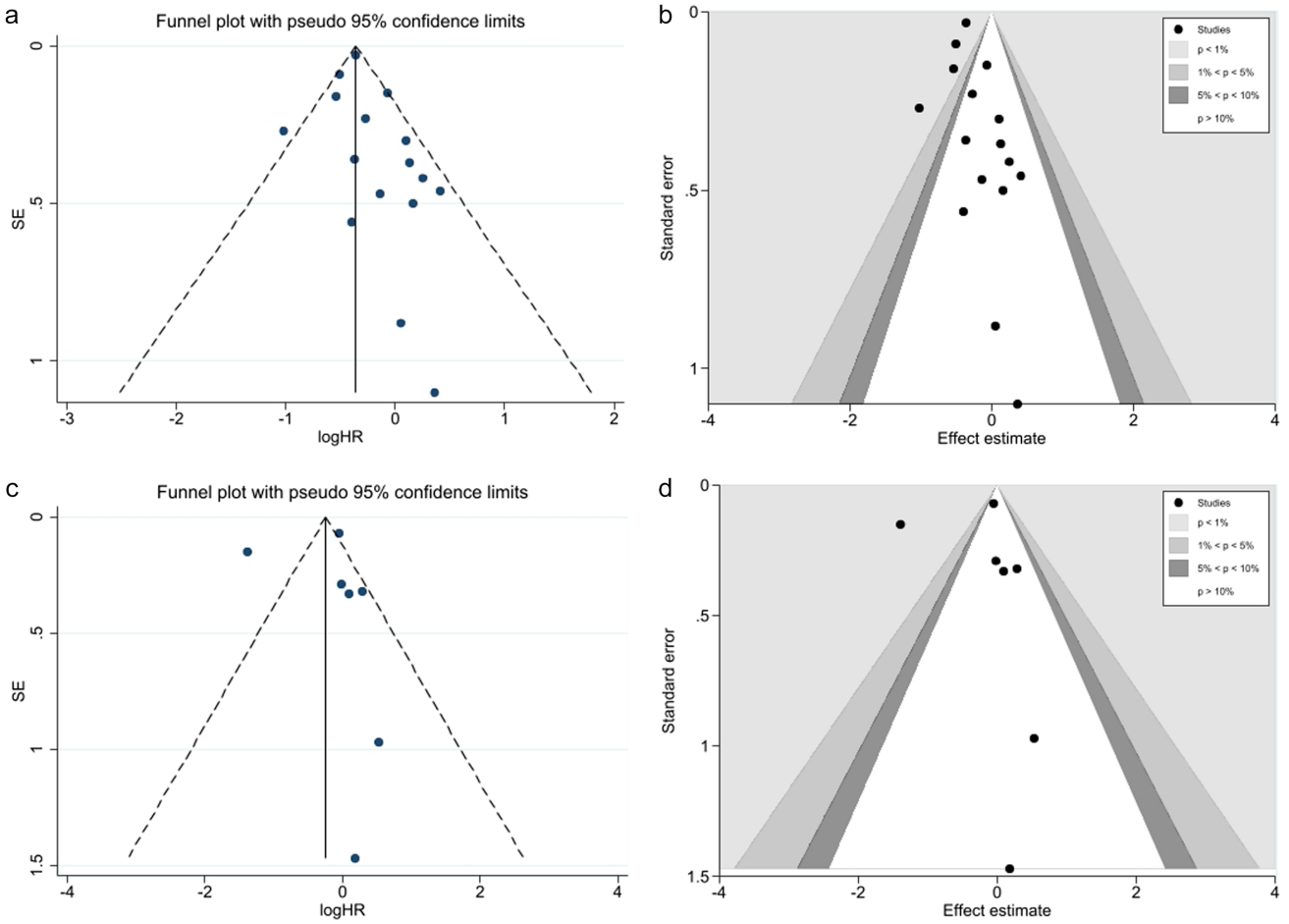

Figure 5 Funnel and contour-enhanced funnel plots of overall survival (a, b) and disease-free survival (c, d).

survival from parametric survival analysis using the Weibull survival distribution. The results demonstrate important outcomes regarding the effect of bridging LRT before LT in the short term, such as 1-year outcomes and non-drop-out survival rate, and in the long term, such as 5-year outcomes and median survival times.

The results demonstrate important outcomes regarding the effect of bridging LRT before LT in the short term, such as 1-year outcomes and non-drop-out survival rate, and in the long term, such as 5-year outcomes and median survival times. Several observational studies revealed that pretransplant LRT decreases waiting-list drop-out, particularly for patients with a long waiting time for LT of more than 6 months, tumor size of more than 3 cm, or multiple nodules.[7,8,17,26] Practically, bridging therapy with pretransplant locoregional treatment is usually performed for patients with high-risk characteristics, especially those with an expected LT schedule longer than 6 months. However, no randomized controlled experiments or meta-analyses have confirmed these findings.

Our study correlates well with the three previous meta-analyses.[5,27,28] Kulik et al. conducted a meta-analysis of cohort studies by screening 4022 studies regarding downstaging and bridging treatments from 1996 to 2016, which yielded 10 studies on OS and 15 studies on DFS analysis. Their results showed that bridging therapy did not affect the OS (HR 1.03, 95% CI 0.75–1.40, $P = 0.76$) and DFS (HR 1.44, 95% CI 0.91–2.29, $P = 0.94$). Unfortunately, they cannot obtain the result in preventing drop-outs due to significant heterogeneity among studies.[5] Despite that, the study was delicately conducted and answered critical clinical questions. The study only gathered data until 2016, while much more updated evidence was published with improving techniques and outcomes as time went by. Therefore, our study helps answer the clinical question in a setting closer to reality. Also, we analyzed the subgroup population to answer what previous authors suggested and left to mention.

Di Martino et al. demonstrated no apparent benefit of bridging LRT in ITT non-RCT cohorts on OS (HR 0.67, 95% CI 0.40–1.12, $P = 0.71$), recurrence rate (HR 0.74, 95% CI 0.17–3.21, $P = 0.69$), and drop-out rate (HR 1.42, 95% CI 0.93–2.16, $P = 0.11$) up to year 2021.[27] However, the analysis focused on only studies with ITT results; only three and four of the six included studies were included in the OS and DFS analyses. The calculation should have included many significant publications,

which may have led to underestimating the treatment effect. While the Di Martino et al. meta-analysis aimed to estimate the impact of bridging therapy on short-term intervals up to a maximum duration of 5 years, our study aimed to find the long-term effect of LRT by constructing the HR by parametric survival analysis and median survival time. In contrast to the pooled HR of drop-outs proportion in Di Martino et al., we estimated the non-dropping-out survival by simulating individual time-to-event patient data first, then used a parametric Weibull regression model to estimate the HR. We used this method to assess the effect of LRT in acquiring the time-to-event result.

Also, another study by Kostakis et al. reported improvement in overall survival at 1-year intervals in the LRT group compared with the non-LRT group (HR 0.54, 95%CI 0.35–0.86, $P = 0.57$). However, the benefit of LRT exists only temporarily, and it eventually loses its benefit at 3- and 5-year time points. Unfortunately, interpreting this study's results should be cautious since there was significant heterogeneity, requiring more bias testing.[28] This could be because the gathered studies, such as Bauschke et al.,[29] included transplant-eligible patients according to either the Milan or the UCSF criteria. In contrast, our meta-analysis included studies with strict inclusion for patients within the Milan criteria only. Thus, we could limit the heterogeneity and enhance confidence in the results.

Our result revealed that the bridging therapy did not improve the OS and DFS after LT in the general population, which could be because bridging therapy has different treatment effects in people with various risks. Therefore, we performed subgroup analysis based on specific characteristics such as long waiting time, high serum AFP levels, and large tumor size. We obtained satisfactory results showing that pre-LT bridging therapy improved survival rates in patients with waiting times longer than 6 months. This finding correlates favorably well with the recommendation of the EASL/EORTC clinical practice guidelines.[30] It offers compelling evidence to use bridging LRT in a transplant program for patients who are likely to be on the waiting list for longer than 6 months. However, the results did not show the advantage of bridging therapy in patients with a waiting time shorter than 3 months. One possible explanation for this finding may be that there is more time to observe the tumor biology and detect distant micro-metastases that might have been missed in radiography during the early follow-up period. Therefore, the bridging LRT procedure should only be performed occasionally in some patients because it does not add to survival benefit. It should be performed in patients with a long-expected waiting time.

Serum AFP levels upon entering the LT waitlist are generally considered a good prognostic predictor. An earlier study revealed that AFP levels of more than 400 ng/mL were associated with less response to bridging LRT.[31] Unfortunately, only two survival studies[9,15] in our cohort examined the pre-waitlist AFP cutoff of more than 400 ng/mL. Another publication showed that AFP levels of more than 100 and 1000 ng/mL before LT resulted in poor post-LT outcomes. However, after analyzing various levels of serum AFP, the results showed no statistical difference in survival among the 1212 patients with elevated serum AFP levels in the present study.

Patients from most of the included studies received their liver grafts predominantly from deceased donors, but not in three studies,[7,9,11] in which they received them mainly from living donors. Most baseline characteristics did not differ from those with DDLT, except for a slightly high MELD score and a long waiting time. The results from these three studies go along with other results from heterogeneity testing. This finding reflects no genuine differences between studies with LDLT and DDLT procedures. Interestingly, patients from Asian countries with most underwent LDLT tend to have better OS but not DFS compared with those from European or North American countries with DDLT preferable. Even though the result was not statistically significant, it does reflect that LDLT can be acceptable as an alternative for DDLT in location settings where deceased graft donors were in shortage. Also, much evidence supports the idea that LDLT can be effectively performed as the DDLT without affecting survival and recurrence outcomes.[30,32]

Our study has many strengths. Even though bridging therapy was routinely incorporated into pre-LT care for patients with risk factors for drop-out, the results revealed the first evidence demonstrating a definite survival benefit of neoadjuvant bridging therapies before LT for only patients with long waiting times. We found a solution for missing data by regenerating the original studies' time-to-event survival data at individual patient levels. This method allowed us to perform the desired secondary analyses. Furthermore, we explored various pretransplant conditions to find a suitable strategy for patient selection.

Nevertheless, our study could have been more extensive in several ways. First, despite a comprehensive search, no randomized controlled trial was available. Secondly, most studies were single-center studies, which could have resulted in selection bias and an exaggerated treatment effect. However, we kept them at a minimum level by applying the I^2 test, funnel plots, and contour-enhanced funnel plot analysis to test for small-study effects or publication bias. The results indicated that there was no publication bias. Third, data regarding neoadjuvant or adjuvant therapy, including systemic treatment and immune checkpoint, were also limited in this meta-analysis. None of the included studies have reported the implication of these treatments in their LT protocol. A possible explanation is that systemic treatment such as sorafenib was shown not to be beneficial to increased DFS; however, it increased the adverse side effects according to the STORM trial.[33] In terms of immune checkpoint treatment, the treatment was proven beneficial for the initial or recurrence of HCC. However, the application of immune checkpoint treatment into the LT protocol was still pending, as were results from the ongoing trials, including PLENTY and DULECT 2020–1. Fourth, estimating the long-term impact of LRT from outcomes during 5-year follow-up data might take a lot of work to conclude and require meticulous methods. Despite this, we postulated the HR from paramedian survival analysis and calculated the median survival time based on this 5-year information. Lastly, given the nature of a meta-analysis study, bias and heterogeneity might have arisen from the original studies. Therefore, we made our best effort to minimize them by conducting careful study selection, transforming data into individual patient data, and performing subgroup analyses. It would be better to gather more specific information, including the adverse events and individual patient details. We want to investigate some particular subgroup populations further, such as the session numbers of LRT or the more in-depth analysis of tumor size and nodules.

Unfortunately, we sometimes could not acquire the original data from the corresponding authors upon inquiry. Most patients in the included studies received LRT for 1–2 sessions. Only very few patients received more than three sessions of LRT, concerning the fact that tumors requiring more than four sessions of the bridging LRTs are likely to have aggressive biology and are associated with poor disease-free survival.[34] Thus, we could not perform a subgroup analysis comparing various interventional protocols, including combination treatment. Unfortunately, we could only retrieve the number of transplant cases due to HCC. This might cause the underestimation of the actual transplant cases from all causes. However, there is no significant heterogeneity between studies with low or high volumes of transplants. Despite these limitations, our meta-analysis could help support decision-makers in endorsing pretransplant bridging LRT for HCC patients with a long waiting time. Randomized, controlled studies on this issue in a controlled environment should be undertaken. With more available data in the future, the treatment effect of LRT in protecting patients from dropping out of the protocol can be estimated.

Conclusion

Our work has demonstrated that bridging LRT benefits patients who are expected to have a long waiting time for LT. However, further studies need to be done to reach conclusions regarding other subgroups. Nevertheless, these results represent an important initial step toward precision medical treatment tailored to each patient with HCC subject.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. PRISMA checklist.
Table S2. Search terms and search strategy.
Table S3. PICO table.