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Original Article

Survival impact of pre-transplant local treatments in liver transplant recipients with BCLC stage A hepatocellular carcinoma

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Abstract: This study aimed to evaluate the impact of different pre-transplant local treatments on the survival of liver transplantation (LTx) recipients with BCLC Stage A Hepatocellular Carcinoma (HCC). We analyzed data from the Taiwan Cancer Registry and National Health Insurance Research Databases spanning 2012 to 2018. Employing propensity score matching, patients were categorized into three groups: those receiving local treatments (180 patients), hepatectomy (179 patients), and combined treatments (180 patients). The primary outcomes were overall mortality and HCC-specific death, assessed using time-varying Cox regression models and Kaplan-Meier survival analysis. During a median follow-up period of 3.92 years, all-cause mortality rates were observed as 74.44% for local treatments, 42.46% for hepatectomy, and 65.00% for combined treatments. HCC-specific mortality rates followed a similar pattern at 65.00%, 39.11%, and 59.44%, respectively. Adjusted hazard ratios demonstrated significantly elevated mortality risks associated with local and combined treatments compared to hepatectomy. Notably, the 2-year overall and HCC-specific survival rates were highest in the hepatectomy group, surpassing those observed in both the combined treatment and local treatment groups. The findings of our study highlight that for patients with BCLC Stage A HCC, undergoing hepatectomy prior to LTx is associated with superior survival outcomes compared to solely local treatments. This underscores the importance of considering hepatectomy as a vital component of the treatment strategy in this patient population.

Keywords: Hepatocellular carcinoma, BCLC stage A, liver transplantation, hepatectomy, local regional therapy

Introduction

Hepatocellular carcinoma (HCC) ranks as the fourth leading cause of cancer-related deaths globally [1, 2]. Its main risk factors encompass viral hepatitis, alcohol-related liver disease (ALD), and nonalcoholic liver diseases. HCC's complexity stems from its neoplastic pathology and the cirrhotic liver environment caused by chronic inflammation. Notably, HCC is the pri-

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mary cause of mortality in patients with cirrhosis [3]. Clinically, HCC is stratified using various staging systems, such as the American Joint Committee on Cancer (AJCC) TMN stage [4], the Barcelona Clinic Liver Cancer (BCLC) classification [5], and the Okuda stage [6]. Among these, the BCLC staging system, which encapsulates both tumor burden and liver cirrhosis condition, is renowned for its clinical pertinence and comprehensive scope. Patients in BCLC stage 0 have a five-year survival rate of up to 80%, whereas those in BCLC stage A have a survival rate between 50-60% [7]. The heterogeneity within BCLC stage A, characterized by larger tumor sizes and multiple nodules, necessitates variable treatment approaches. Curative interventions like hepatectomy and radiofrequency ablation (RFA) are the mainstay treatments for early-stage HCC according to BCLC guidelines [8]. Moreover, alternative therapeutic modalities include transcatheter arterial chemoembolization (TACE), radioembolization, and percutaneous ethanol injection (PEI).

While hepatectomy and RFA for HCC offer superior overall survival outcomes in patients with well-preserved liver function, intrahepatic tumor recurrence post-treatment remains a significant risk factor for cancer mortality in these patients [9]. Liver transplantation (LTx), however, has shown to yield superior five-year survival rates compared to other curative therapies [10], particularly in patients adhering to the Milan and UCSF criteria. In such cases, five-year survival rates exceed 70%, with recurrence rates ranging between 10% and 15% [11, 12]. This improved outcome is primarily due to the complete removal of the cirrhotic liver, a potential site for future tumor development. Nonetheless, the fraction of BCLC stage A HCC patients undergoing LTx is relatively low compared to those receiving RFA or hepatectomy. This trend is attributed to the elevated surgical mortality risks and the scarcity of donor organs associated with LTx. Therefore, other curative interventions like hepatectomy or RFA are frequently considered before LTx in the treatment hierarchy.

The efficacy of radiofrequency ablation (RFA) versus hepatectomy for early-stage hepatocellular carcinoma (HCC) remains debated. Some studies find no significant difference in survival outcomes between these modalities [13, 14], while more recent evidence points to superior disease-free survival and a higher five-year overall survival rate associated with surgical intervention compared to RFA [15-18]. Additionally, when contrasting with other local treatments like transcatheter arterial chemoembolization (TACE), hepatectomy consistently demonstrates more favorable results [19]. Notably, these studies have predominantly concentrated on the immediate outcomes of overall and disease-free survival, with scant data regarding the influence of initial treatment choice for BCLC stage A HCC on survival following salvage LTx. Our study, a comprehensive nationwide population-based analysis, aims to address this gap. Employing propensity score matching, we seek to ascertain the most effective initial treatment strategy for BCLC stage A HCC patients who may subsequently require LTx.

Patients and methods

Study cohort

This cohort study utilized patient data extracted from the Taiwan Cancer Registry Database (TCRD) and the National Health Insurance Research Database (NHIRD), spanning the period from January 1, 2012, to December 31, 2018. The study population consisted of individuals diagnosed with HCC who underwent LTx. The index date in this study was defined as the date of LTx, and the follow-up period extended until December 31, 2020. The TCRD, managed by the Collaboration Center of Health Information Application, provided comprehensive information on cancer patients, including clinical stage, treatment modalities, chemotherapy regimens, pathology, and surgical procedures [20-22]. The study protocols received approval from the Institutional Review Board of Tzu-Chi Medical Foundation (IRB109-015-B).

Inclusion and exclusion criteria

To ensure study eligibility, specific criteria were applied to the patient selection process. Inclusion criteria encompassed patients aged 18 years or older, with a confirmed diagnosis of HCC and classified as BCLC stage A, indicating their suitability for LTx. Exclusion criteria comprised patients with a prior history of other cancers, distant metastasis, missing sex data, age below 18, ambiguous staging, or non-hepatocellular carcinoma cases. Individuals present-

ing severe liver dysfunction, heart disease, renal failure, or other significant comorbidities that contraindicate LTx were excluded from the study. Moreover, patients affected by severe immune system disorders, or organ failure were also excluded from participation.

A comprehensive comparative study is warranted to determine the optimal pre-transplant local treatment strategy for LTx recipients diagnosed with BCLC Stage A HCC and its impact on overall survival. The "local treatments" group includes interventions such as radiofrequency ablation (RFA), transarterial chemoembolization (TACE), radiotherapy (RT), and percutaneous ethanol injection (PEI). We will ensure this definition is consistently used throughout the manuscript. This study aims to evaluate the effectiveness of distinct pre-transplant treatment strategies for patients undergoing liver transplantation (LTx). The treatment groups are: (1) patients receiving local treatments such as RFA, TACE, RT, or PEI; (2) patients undergoing hepatectomy; and (3) patients receiving a combination of local treatments and hepatectomy. Furthermore, we ensured that all enrolled patients attended regular outpatient follow-up visits at least every three months throughout the study period.

Currently, the optimal management strategy before LTx for BCLC Stage A HCC remains uncertain, leading to ambiguity regarding the treatment approach associated with the most favorable overall survival outcomes. Thus, conducting a comprehensive comparative study will significantly contribute to enhancing our understanding of the most effective treatment approach in this specific patient population.

Propensity score matching

In order to account for potential confounding factors when comparing the survival outcomes among the pre-transplant local treatment groups in LTx recipients with BCLC Stage A HCC, a propensity score matching (PSM) method was employed. Patient matching was based on variables including age, sex, income levels, LTx centers, urbanization, Charlson Comorbidity Index (CCI) scores, and other comorbidities (such as diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease, cardiovascular diseases, chronic obstructive pulmonary disease, and alcohol liver disease), as indicated in **Table 1**. The matching process resulted in a 1:1 ratio for each group, utilizing the greedy matching method with a caliper of 0.1 [23]. Comorbidities were identified by employing ICD-9-CM or ICD-10-CM codes for the primary diagnoses recorded in inpatient records or outpatient visits occurring at least twice within a one-year period. Continuous variables were presented as means ± standard deviations, where applicable.

Outcome measures

The primary objective of this study was to assess and compare the overall mortality rate among LTx recipients with BCLC Stage A HCC across distinct pre-transplant local treatment groups. Tumor recurrence or metastasis represents a prominent cause of mortality following LTx in HCC patients. Although LTx is an effective treatment for primary liver cancer, it does not completely eradicate the presence of existing or potential metastatic lesions. Hence, the risk of tumor recurrence or metastasis persists even after the transplantation procedure. As a result, our investigation also places emphasis on a secondary outcome of interest, specifically HCC-specific death, which specifically examines mortality attributed to HCC. This comprehensive evaluation endeavors to provide valuable insights into the overall survival outcomes and the specific impact of HCC on post-transplantation mortality.

Statistical analysis

We assessed the association between survival outcomes and distinct pre-transplant local treatment groups among LTx recipients with BCLC Stage A HCC. To account for potential confounding factors, such as age, sex, income levels, urbanization, CCI scores, and other comorbidities, we employed time-varying Cox regression models. In our analysis, we incorporated a time-varying covariate that captured the interval between HCC diagnosis and LTx [24, 25]. This covariate provided valuable insights into disease progression and treatment timing, both of which could significantly impact the primary outcome of interest, namely all-cause mortality. By dividing the follow-up time into intervals and assessing covariate values at specific time points, our Cox regression models estimated hazard ratios (HR) or coefficients associated with these time-varying covariates.

Table 1. Characteristics of liver transplant recipients with BCLC stage A hepatocellular carcinoma (HCC) and different pre-transplant local treatments (after propensity score matching)

	Local treatments (RFA, TACE, RT, or PEI)		Hepatectomy		Local treatments and hepatectomy		*P*
	N=180		N=179		N=180		
	N	%	N	%	N	%	
Age (mean ± SD)	61.89 ± 12.03		60.45 ± 13.22		60.44 ± 12.59		0.4534
Age, Median (IQR, Q1, Q3)	62.65 (54.30, 70.54)		62.96 (52.47, 69.67)		60.44 (52.11, 69.97)		0.7271
Age group, years							0.8039
≤55	48	26.67%	55	30.73%	56	31.11%	
56-65	55	30.56%	50	27.93%	53	29.44%	
66-75	57	31.67%	60	33.52%	51	28.33%	
>75	20	11.11%	14	7.82%	20	11.11%	
Sex							0.4493
Female	46	25.56%	53	29.61%	43	23.89%	
Male	134	74.44%	126	70.39%	137	76.11%	
Income levels (NTD)							0.9653
Low income	0	0.00%	2	1.12%	1	0.56%	
Financially dependent	47	26.11%	43	24.02%	49	27.22%	
≤20,000	56	31.11%	56	31.28%	49	27.22%	
20,001-30,000	10	5.56%	11	6.15%	12	6.67%	
30,001-45,000	12	6.67%	13	7.26%	15	8.33%	
>45,000	55	30.56%	54	30.17%	54	30.00%	
Liver Transplant Centers							0.6384
Liver Transplants in Taiwan	119	66.11%	113	63.13%	114	63.33%	
Liver Transplants Outside Taiwan	61	33.89%	66	36.87%	66	36.67%	
Urbanization							0.7447
Rural	53	29.44%	52	29.05%	47	26.11%	
Urban	127	70.56%	127	70.95%	133	73.89%	
CCI Scores							0.3956
0	5	2.78%	10	5.59%	9	5.00%	
≥1	175	97.22%	169	94.41%	171	95.00%	
CCI Scores							
Congestive Heart Failure	8	0.0444	6	0.0335	11	0.0611	0.4566
Dementia	3	1.67%	0	0.00%	4	2.22%	0.1539
Chronic Pulmonary Disease	34	18.89%	35	19.55%	21	11.67%	0.0843
Rheumatic Disease	2	1.11%	3	1.68%	0	0.00%	0.2415
DM with complications	13	7.22%	16	8.94%	13	7.22%	0.1460
Hemiplegia and Paraplegia	0	0.00%	0	0.00%	0	0.00%	0.9999
Renal Disease	11	6.11%	9	5.03%	15	8.33%	0.4317
AIDS	0	0.00%	0	0.00%	0	0.00%	0.9999
Other comorbidities							
DM	47	26.11%	45	25.14%	53	29.44%	0.7859
Hypertension	102	56.67%	90	50.28%	95	52.78%	0.5014
Hyperlipidemia	34	18.89%	34	18.99%	38	21.11%	0.7648
Cardiovascular diseases	62	34.44%	55	30.73%	60	33.33%	0.7452
COPD	38	21.11%	45	25.14%	46	25.56%	0.6996
Alcohol liver disease	17	9.44%	13	7.26%	17	9.44%	0.8520
Outcomes							
All-cause Death	134	74.44%	76	42.46%	117	65.00%	<0.0001
HCC Death	117	65.00%	70	39.11%	107	59.44%	<0.0001

Abbreviations: HCC, Hepatocellular Carcinoma; RFA, Radiofrequency Ablation; TACE, Transcatheter Arterial Chemoembolization; RT, Radiotherapy; PEI, Percutaneous Ethanol Injection; N, Number; IQR, Interquartile Range; NTD, New Taiwan Dollars; DM, Diabetes Mellitus; COPD, Chronic Obstructive Pulmonary Disease; CCI, Charlson Comorbidity Index; AIDS, Acquired Immunodeficiency Syndrome; SD, Standard Deviation.

Table 2. Time-varying cox proportional model analysis of all-cause death and HCC-specific death in liver transplant recipients with BCLC stage A hepatocellular carcinoma (HCC) and different pre-transplant local treatments

	HR (95% CI)	*P*	aHR* (95% CI)	*P*
All-Cause Death				
Hepatectomy (Ref.)	1.00	-	1.00	-
Local treatments (RFA, TACE, RT, or PEI)	3.08 (2.32, 4.1)	<0.0001	6.53 (3.93, 10.83)	<0.0001
Local treatments and hepatectomy	2.37 (1.77, 3.18)	<0.0001	3.67 (2.63, 5.14)	<0.0001
HCC-Specific Death				
Hepatectomy (Ref.)	1.00	-	1.00	-
Local treatments (RFA, TACE, RT, or PEI)	3.37 (2.46, 4.61)	<0.0001	7.14 (4.18, 12.18)	<0.0001
Local treatments and hepatectomy	2.82 (2.06, 3.87)	<0.0001	4.39 (3.06, 6.29)	<0.0001

Abbreviations: HCC, Hepatocellular Carcinoma; HR, Hazard Ratio; aHR, Adjusted Hazard Ratio; CI, Confidence Interval; RFA, Radiofrequency Ablation; TACE, Transcatheter Arterial Chemoembolization; RT, Radiotherapy; PEI, Percutaneous Ethanol Injection; Ref., Reference group. Footnote: *All covariates in **Table 1** were adjusted using a time-varying Cox proportional model. The time-varying covariate in this study is the interval between the diagnosis of HCC and liver transplant. The index date in the study refers to the date of liver transplant.

These estimates enabled us to quantify the effects of these covariates on the risk of all-cause mortality. Incorporating these time-varying covariates and coefficients allowed us to comprehensively account for their dynamic nature and their influence on the outcome over time, thus enhancing our understanding of the factors contributing to all-cause mortality in the context of LTx for HCC patients.

Furthermore, we conducted an additional analysis to estimate the risk of mortality within the pre-transplant local treatment groups. To achieve this, we employed the Kaplan-Meier method to estimate mortality rates, and the stratified log-rank test was used to compare mortality curves across the groups. All statistical analyses were performed using SAS version 9.4.

Results

The present study initially included 1,990 patients with HCC who underwent LTx before PSM. Following 1:1 PSM, a total of 719 patients were retained across the three different pre-transplant local treatment groups. Specifically, these groups consisted of 180 patients who received local treatments (such as RFA, TACE, RT, or PEI), 179 patients who underwent hepatectomy, and 180 individuals who underwent both local treatments and hepatectomy prior to LTx. After PSM, an equal number of patients were included in each group, and baseline characteristics such as age, sex, income levels, urbanization, LTx centers, CCI scores, and other comorbidities were balanced between the groups (**Table 1**).

During the median follow-up of 3.92 years, crude all-cause mortality rates were 74.44% for patients who received local treatments, 42.46% for those who underwent hepatectomy, and 65.00% for those who received both local treatments and hepatectomy before LTx (P<0.0001), respectively. Similarly, the HCC-specific mortality rates were 65.00% for patients who received local treatments, 39.11% for those who underwent hepatectomy, and 59.44% for individuals who underwent both local treatments and hepatectomy before LTx (P<0.0001), respectively (**Table 1**).

The results of the Time-Varying Cox Proportional Model analysis examining the association between different pre-transplant local treatments and the risk of all-cause death and HCC-specific death in LTx recipients with BCLC Stage A HCC are summarized in **Table 2**. The aHRs for all-cause mortality were 3.67 (95% CI: 2.63, 5.14) for local treatments plus hepatectomy, and 6.53 (95% CI: 3.93, 10.83) for local treatments, compared to patients who received hepatectomy before LTx for BCLC Stage A HCC. Similarly, the aHRs for HCC-specific death were 4.39 (95% CI: 3.06, 6.29) for local treatments plus hepatectomy, and 7.14 (95% CI: 4.18, 12.18) for local treatments, compared to patients who received hepatectomy before LTx for BCLC Stage A HCC. These findings suggest

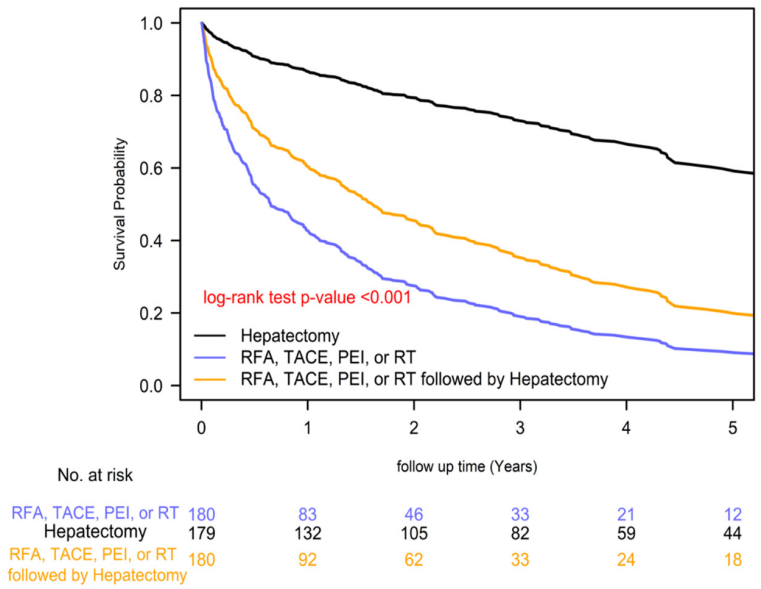

Figure 1. Kaplan-Meier overall survival curves of liver transplant recipients with BCLC stage A hepatocellular carcinoma (HCC) and different pre-transplant local treatments.

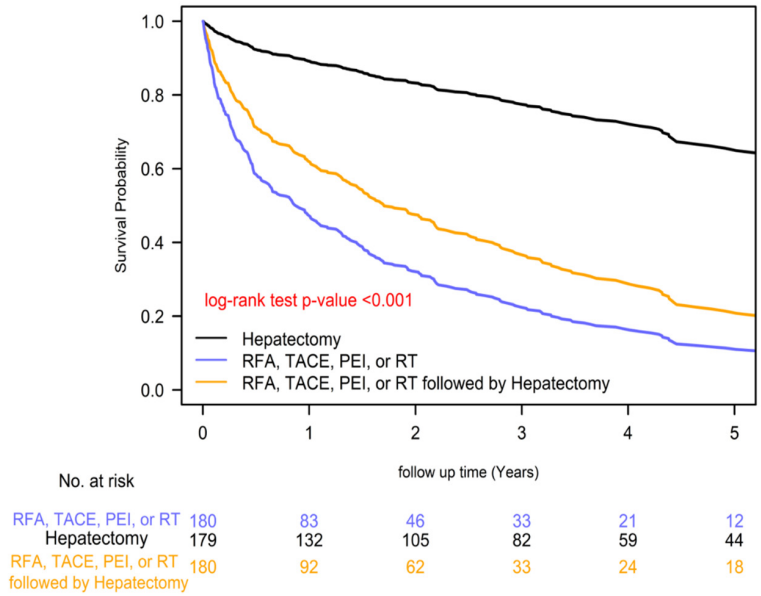

Figure 2. Kaplan-Meier HCC-specific survival curves of liver transplant recipients with BCLC stage A hepatocellular carcinoma (HCC) and different pre-transplant local treatments.

The 2-year overall survival rates differed significantly among the distinct pre-transplant local treatment groups, with rates of 84.88% for hepatectomy, 57.91% for local treatments plus hepatectomy, and 38.30% for local treatments prior treatments groups (P= 0.0001; **Figure 1**). Similarly, the 2-year HCC-specific survival rates also varied significantly among the groups, with rates of 85.90% for hepatectomy, 59.11% for local treatments plus hepatectomy, and 39.09% for local treatments prior treatments groups (P= 0.0001; **Figure 2**). These results suggest that pre-transplant hepatectomy is associated with improved survival compared to other treatments. Among the different treatment groups prior LTx, the order of superior survival was as follows: hepatectomy, combined local treatments and hepatectomy, and local treatments.

Discussion

Our study reveals that pre-transplant hepatectomy, when employed as the initial intervention for BCLC stage A HCC, confers enhanced outcomes in reducing both all-cause and HCC-specific mortality in subsequent LTx scenarios. This superiority holds when compared to either local treatments alone or a combined regimen of local treatments and hepatectomy, as detailed in **Table 2** and illustrated in **Figures 1** and **2**.

that local treatments and combined local treatments with hepatectomy are associated with significantly increased risks of all-cause mortality and HCC-specific death compared to hepatectomy in pre-LTx recipients with BCLC Stage A HCC.

While LTx demonstrates a lower recurrence rate compared to hepatectomy for HCC [26], it is challenged by organ scarcity, heightened surgical mortality, and the risk of patients being removed from the waiting list. In light of these challenges, salvage LTx has emerged as a via-

ble alternative [27]. Various studies have evaluated primary versus salvage LTx. Despite variability in results from several meta-analyses, the general consensus is that salvage LTx is a safe and feasible option [28, 29].

The selection between RFA and hepatectomy for early-stage HCC remains contentious. Feng et al. reported that RFA is not inferior to hepatectomy for small HCCs [13]. Conversely, a Korean study indicated similar overall survival rates for both treatments, but better disease-free survival (DFS) with hepatectomy [30]. Recent evidence increasingly favors surgical intervention, showing not only better progression-free survival but also enhanced overall survival outcomes compared to ablation therapy [15-18]. A randomized control trial suggested that repeat hepatectomy might offer improved local disease control and long-term survival relative to RFA, particularly in patients with larger HCCs or elevated AFP levels [31]. Additionally, another study highlighted that for patients with microvascular invasion (MIV), hepatectomy is preferred over RFA even for tumors smaller than 3 cm [32].

These findings highlight the critical role of pre-salvage transplantation strategy in managing HCC patients eligible for LTx. Given the biological heterogeneity of HCC, some tumors at BCLC stage A may exhibit a more aggressive nature and harbor occult metastasis, potentially escaping complete eradication by local treatments [33, 34]. This incomplete tumor removal can lead to increased HCC-related mortality following LTx. HCC tumors, particularly smaller ones, may demonstrate a micro-metastasis pattern with invasion into the portal vein branches [33, 34]. In this context, hepatectomy, and specifically anatomic liver resection, offers a more effective means of removing potential tumor spread along these branches compared to RFA [30]. RFA, especially in larger tumors requiring multiple ablations, often struggles to achieve clear margins, increasing the likelihood of residual viable tumor cells [18, 35]. This observation is particularly pertinent in our cohort, where patients initially diagnosed with early-stage HCC and treated with hepatectomy or other local treatments eventually required LTx. This progression suggests a predisposition towards more aggressive HCC variants in this group.

In identifying high-risk HCC patients, factors such as larger tumor diameters, multiple nodules, or elevated AFP levels are pivotal [36]. Our study demonstrates that for BCLC stage A HCC patients, hepatectomy as the initial treatment with curative intent or as a bridge therapy prior to LTx yields superior survival outcomes compared to local treatments. Particularly for BCLC stage A patients at elevated risk of recurrence, hepatectomy emerges as a logical first-line therapy, especially when subsequent LTx is contemplated.

Consistent with other studies, our research confirms a stable overall survival rate for patients undergoing hepatectomy [29]. However, the survival rate for our local treatment group was markedly lower (**Table 2**; **Figures 1** and **2**). A meta-analysis indicated that patients receiving locoregional therapy followed by salvage LTx exhibited a less favorable overall survival rate than those undergoing primary LTx [37]. In our study, the precise pre-transplantation tumor status remains unspecified since the BCLC stage A stage was based on the index date. Consequently, it is plausible that tumors in patients of the local treatment group were in more advanced stages at the time of LTx.

This study has several limitations. First, the data were sourced from the Taiwan Cancer Registry Database, which lacks detailed tumor characteristics such as precise size, number, and specific locations. Moreover, the exact tumor status of patients before LTx is not available. Second, the retrospective design introduces inherent biases. To address potential confounding factors, we employed PSM based on variables such as age, sex, income levels, LTx centers, urbanization, CCI scores, and various comorbidities, including diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease, cardiovascular diseases, chronic obstructive pulmonary disease, and alcohol liver disease, which reflect lifestyle factors. Additionally, we ensured that all enrolled patients had regular outpatient follow-up visits at least every three months during the study period. This regular follow-up schedule demonstrated good adherence to treatments and helped minimize the impact of non-compliance on the study outcomes. Despite these efforts, the retrospective nature may still influence the find-

ings. Future prospective studies are needed to provide a more detailed comparison of treatment outcomes.

Conclusion

Our study represents a pioneering effort to assess the optimal local treatments preceding LTx, and it uncovers that hepatectomy, when utilized as the initial treatment for BCLC stage A patients who later undergo LTx, leads to enhanced post-transplantation survival outcomes compared to those receiving other local treatments. This finding is particularly salient for patients categorized as BCLC stage A yet potentially earmarked for future LTx. In such scenarios, hepatectomy should be prioritized as the primary treatment with curative intent or as an effective bridging therapy. This approach could significantly influence clinical decision-making and patient management strategies in hepatocellular carcinoma care.

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Disclosure of conflict of interest

None.

Abbreviations

HCC, Hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; LTx, Liver transplant; DTLT, deceased donor Liver transplant; LDLT, living donor Liver transplant; RFA, radiofrequency ablation; TACE, trans-arterial chemoembolization; BCLC, Barcelona classification of liver Cancer; AJCC, American Joint Committee on Cancer.

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