Journal of Hepatocellular Carcinoma Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

ALBI Grade Analyses of TACE Combined with Anti-Angiogenesis Therapies Plus PD-1 Inhibitors versus Anti-Angiogenesis Therapies Plus PD-1 Inhibitors in Advanced HCC

Xin Hong[1,*], Di Hu[2,*], Wen-Jie Zhou[3,*], Xiu-De Wang[4], Li-Hua Huang[5], Tian-An Huang[1], Yi-Wei Guan[1], Jingyu Qian[6], Wen-Bin Ding[1]

[1]Department of Interventional Radiology, Affiliated Hospital 2 of Nantong University, Nantong, People's Republic of China; [2]Department of Interventional Radiology, The First Affiliated Hospital of Soochow University, Suzhou, People's Republic of China; [3]Department of Interventional Radiology, Northern Jiangsu People's Hospital, Clinical Medical College of Yangzhou University, Yangzhou, People's Republic of China; [4]Department of Interventional Radiology, Nantong Second People's Hospital, Nantong, People's Republic of China; [5]Department of Interventional Radiology, Nantong Haimen District People's Hospital, Nantong, People's Republic of China; [6]Department of Interventional Radiology, The First Affiliated Hospital of Bengbu Medical University, Bengbu, People's Republic of China

*These authors contributed equally to this work

Correspondence: Wen-Bin Ding, Department of Interventional Radiology, Affiliated Hospital 2 of Nantong University, Nantong, 226001, People's Republic of China, Tel/Fax +86 15951302169, Email 15951302169@163.com; Jingyu Qian, Department of Interventional Radiology, the First Affiliated Hospital of Bengbu Medical University, Bengbu, 233004, People's Republic of China, Tel/Fax +86 13004081388, Email jyqian1388@163.com

Objective: To evaluate the baseline albumin-bilirubin (ALBI) grade's role in advanced hepatocellular carcinoma (HCC) receiving transarterial chemoembolization (TACE) plus anti-angiogenesis therapies and PD-1 inhibitors (TACE+TP) versus anti-angiogenesis therapies and PD-1 inhibitors (TP).

Methods: This multicenter retrospective study enrolled advanced HCC undergoing TACE+TP or TP from January 2019 to June 2023 at three hospitals in China. The primary outcomes were time to progression of the ALBI grade and change in ALBI score between the initial baseline and the final assessment point available, the secondary outcomes consisted of overall survival (OS) as well as progression-free survival (PFS).

Results: One hundred and eighty-three patients were ultimately enrolled in this study for analysis, of whom 44 were categorized as having an ALBI grade 1 (TACE+TP, n = 23; TP, n = 21) and 139 were classified as ALBI grade 2 (n = 77; n = 62). Time to progression of the ALBI grade, indicating liver function deterioration, was comparable between the TACE+TP and TP groups (median, 11.2 vs 19.3 months; P = 0.353). Change in ALBI score between the initial baseline and the final assessment point available was comparable among the two groups (difference in least squares mean, 0.084). Irrespective of the initial ALBI grade, patients in TACE+TP group exhibited a significant enhancement in OS and displayed a promising trend towards better PFS.

Conclusion: TACE+TP had no negative influence on liver function and enhanced survival regardless of baseline ALBI grade when compared to TP in advanced HCC patients.

Keywords: albumin-bilirubin grade, hepatocellular carcinoma, TACE, anti-angiogenesis therapies, PD-1 inhibitors

Introduction

Liver cancer ranks among the most prevalent risk of cancer-related deaths globally, with hepatocellular carcinoma (HCC) accounting for 75–85% of all diagnosed cases.[1,2] Despite advancements in early detection methods for HCC, approximately 80% of individuals are still identified as having intermediate-to-advanced stages upon initial evaluation in the majority of regions globally.[3,4] Transarterial chemoembolization (TACE) stands as the frontline therapy recommended by

Received: 6 July 2024
Accepted: 5 December 2024
Published: 19 December 2024

the Barcelona Clinic Liver Cancer (BCLC) staging system for patients with intermediate-stage HCC. Moreover, TACE is frequently utilized in clinical practice to treat advanced HCC.[3,5–7]

The CHANCE001 study demonstrated that TACE plus PD-(L)1 inhibitors and anti-angiogenesis therapies yielded significantly superior clinical outcomes for advanced HCC compared to TACE alone in real-world clinical scenarios.[8] Meanwhile, the EMERALD-1 Phase III trial demonstrated that TACE plus durvalumab and bevacizumab strongly improved progression-free survival (PFS) versus TACE monotherapy to manage unresectable HCC.[9] Furthermore, a Phase II study, assessing the effectiveness and safety of TACE plus lenvatinib and sintilimab in advanced HCC, showed favorable antitumor potential with a tolerable safety profile.[10] Furthermore, some studies have indicated that the combination of TACE plus PD-1 inhibitors and anti-angiogenesis therapies correlated with enhanced OS when compared to dual systemic treatment being the primary therapy approach for unresectable HCC.[11–13]

The underlying liver function is a critical determinant of patient's prognosis.[14] Assessment of liver function is typically based on established markers, including the Child-Pugh (CP) classification as well as the Albumin-Bilirubin (ALBI) grading system.[15] The ALBI grade offers a superior objective evaluation of liver function versus the CP classification, with demonstrated efficacy that is equivalent to or surpasses that of the CP class.[15] The baseline ALBI classification serves as a critical prognostic marker for HCC patients undergoing surgical resection,[16] sorafenib,[17] lenvatinib,[18] and atezolizumab plus bevacizumab.[19] Beyond its prognostic significance, ALBI grading offers a nuanced assessment of hepatic function throughout the course of treatment for advanced HCC patients.[20] Nevertheless, the influence of baseline ALBI classification on the therapeutic benefits of advanced HCC patients receiving TACE plus anti-angiogenesis therapies and PD-1 inhibitors remains to be definitively established. Consequently, the design of the current study was to evaluate the ALBI grade's role in advanced HCC undergoing TACE plus anti-angiogenesis therapies and PD-1 inhibitors versus anti-angiogenesis therapies plus PD-1 inhibitors.

Materials and Methods

With ethical approval granted by the institutional review board of Affiliated Hospital 2 of Nantong University (No. 2022KT269), this study was performed under the principles of the Declaration of Helsinki. Considering the research's retrospective design, the need for informed consent from participants was waived, and we stated that patient data was strictly confidential, aligning with standard procedures for such research. Advanced HCC treated with TACE plus anti-angiogenesis therapies and PD-1 inhibitors (TACE+TP group) or anti-angiogenesis therapies plus PD-1 inhibitors (TP group) between January 2019 and June 2023 at three hospitals were enrolled. A multidisciplinary discussion was performed before treatment to assess whether TACE+TP or TP alone would be the most appropriate treatment option for the patient. The potential advantages and disadvantages of both treatments were explained to the patients. The final decision on the treatment choice was made by the patients or their relatives. The study's inclusion criteria included: 1) confirmation of the diagnosis of HCC, either through histological examination or clinical assessment; 2) an identifiable lesion, including multinodular HCC; 2) BCLC stage C; 4) patients with HCC-related therapy histories such as curative resection, ablation, or TACE were permitted. 5) CP grade A or B; 6) Administration of anti-angiogenesis agents and PD-1 inhibitors was begun within a four-week window before or subsequent to TACE in the TACE+TP group and PD-1 inhibitors were introduced within four weeks after the commencement of anti-angiogenesis agents in the TP group. Patients lacking complete follow-up data or with missing information were excluded.

TACE Procedure

Patients in the study were treated with two types of TACE: conventional TACE or drug-eluting beads TACE, with procedural details reported in earlier studies.[21] Briefly, all TACE procedures in this study were expertly executed using super-selective chemoembolization by interventional physicians with extensive experience. Repeated TACE was performed based on the "on demand" mode. Evaluation for repeated TACE was performed if contrast-enhanced CT/MRI presented progression of the treated lesion(s) or new lesions for the patient. Repeated TACE was considered until: 1) liver function deteriorated to CP-C; 2) Eastern Cooperative Oncology Group (ECOG) performance status >2; and 3) progression of targeted intrahepatic lesions after three consecutive TACE sessions.

Administration of Anti-Angiogenesis Agents and PD-1 Inhibitors

Anti-angiogenesis agents and PD-1 inhibitors, including combinations of sorafenib/lenvatinib with camrelizumab, or bevacizumab with sintinimab, were started in close proximity to TACE therapy, specifically within a one-month timeframe before or after the procedure. Dosing of camrelizumab or sintinimab at 200 mg was performed intravenously at three-week intervals. Patients received oral sorafenib at 800 mg or lenvatinib dosed at 8 mg for those weighing less than 60 kg and 12 mg for those over 60 kg, with daily administration recommended. Bevacizumab was given intravenously at a dose of 15 mg/kg, also on a three-weekly schedule. In cases of disease progression or intolerable adverse events that persist despite dose reduction, treatment was escalated to regorafenib, considering the individual patient's clinical status and treatment preferences. Apart from anti-tumor therapies, antiviral therapies with entecavir or tenofovir were recommended for patients with detectable HBV-DNA or positive hepatitis B surface antigen (HBsAg) through the entire duration of treatment for HCC.

Assessments and Outcomes

Imaging surveillance was conducted using contrast-enhanced CT and/or MRI at intervals of 2 to 3 months to monitor tumor response and progression. Laboratory assessments were completed prior to each therapy and at regular follow-up visits to evaluate individuals' health status. Whenever serious complications developed or patients experienced discomfort and required a hospital visit for follow-up, they were instructed to return to the hospital. Furthermore, all patients underwent continuous follow-up, concluding either upon their death or the study's endpoint on December 31, 2023. Assessment of imaging response was conducted following the current Modified Response Evaluation Criteria in Solid Tumors (mRECIST), with evaluations performed independently by two senior radiologists at each involved medical center.[22] ALBI scores were calculated using the formula: (log10 bilirubin [in μmol/L] × 0.66) + (albumin (in g/L) × −0.085). ALBI grading is classified into three levels: grade 1 for scores ≤ −2.60, grade 2 for scores > −2.60 to ≤ −1.39, and grade 3 for scores > −1.39.[15]

The primary outcomes were time to progression of the ALBI grade and change in ALBI score between the initial baseline and the final assessment point available. Time to progression of the ALBI grade was measured between the ALBI assessment at baseline and the first subsequent measurement that indicated an increase of at least one grade above the baseline level. The secondary outcomes encompassed overall survival (OS) and PFS. OS was identified as the duration from the commencement of the initial treatment to death due to any cause. PFS was identified as the interval between the start of the initial therapy and the earliest occurrence of tumor progression or death due to any cause.

Statistical Analysis

The patient characteristics were reported utilizing means with standard deviations for continuous data, and utilizing frequencies with percentages for categorical data. Student's *t* test was applied to analyze continuous data. Fisher exact test or the χ^2 test was applied to analyze categorical data. The correlation between change in ALBI score from the initial assessment to the final available evaluation and treatment was evaluated utilizing analysis of Covariance (ANCOVA). ANCOVA was employed to ascertain whether the average changes in ALBI scores, when adjusted for the baseline scores, were consistent between the two treatment cohorts, thereby statistically controlling for the initial ALBI score's impact. The ANCOVA model yielded adjusted least squares means for each treatment group, accounting for the baseline ALBI score's influence. The differences in these adjusted means between the two treatment arms, along with their respective 95% CIs, were reported to provide a comprehensive statistical comparison. OS and PFS were evaluated utilizing the Kaplan–Meier method, and survival curves were compared utilizing a Log rank test to assess differences between groups. A two-tailed P-value of less than 0.05 was determined statistically significant. All analyses were performed utilizing SPSS (version 26.0, IBM, New York).

Results

Patient Characteristics

Overall, 183 advanced HCC patients were enrolled in this study, with 100 and 83 patients categorized into the TACE+TP and TP groups, respectively (Figure 1). Data from patients classified with an ALBI classification of 3 were not included in the analysis due to the limited sample size, which precluded a comprehensive evaluation (n = 5). A summary of patient

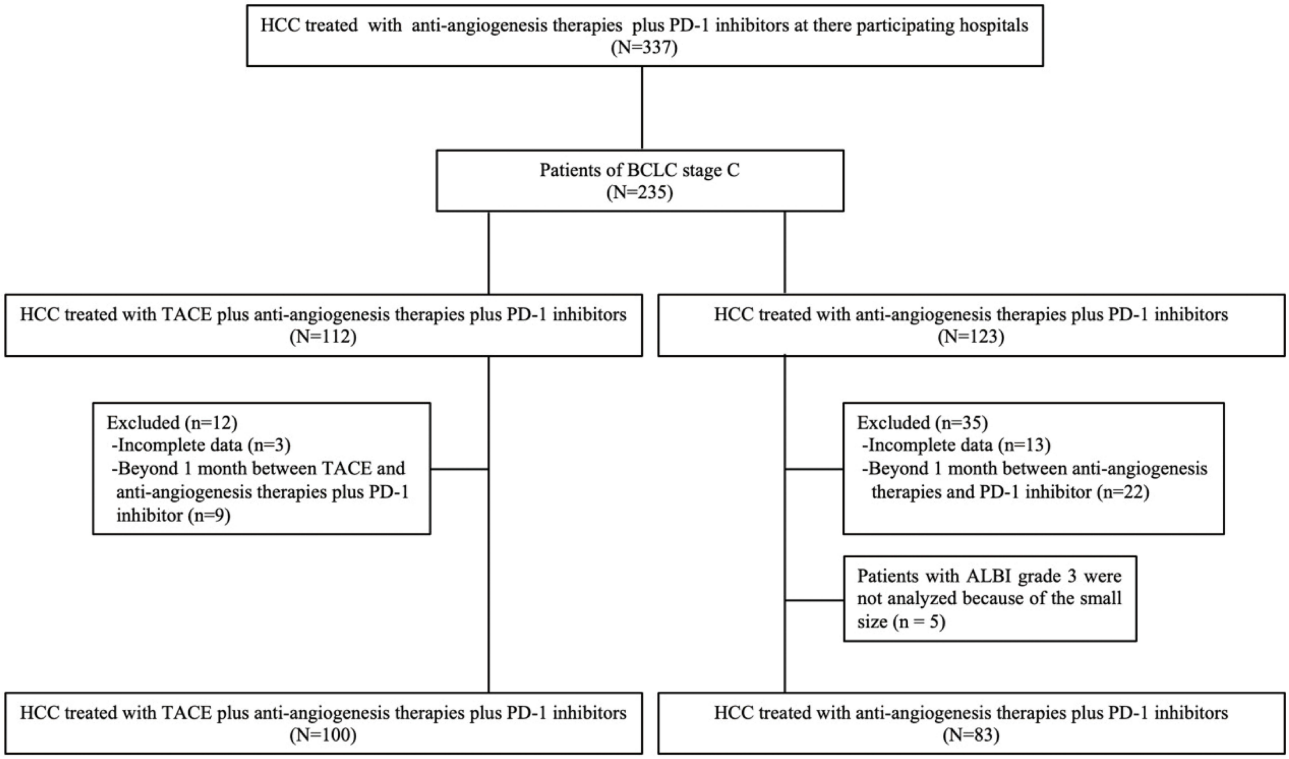

Figure 1 Flowchart of patient selection.
Abbreviations: HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; ALBI, albumin-bilirubin.

characteristics was available in Table 1. Briefly, the majority of the included individuals were male (n = 153, 80.0%), HBV-related HCC (n = 122, 66.7%), and Child-Pugh grade A (n = 139, 76.0%). The baseline characteristics were similar among the two groups.

Of the 183 patients, 44 were categorized as having an ALBI grade 1 (TACE+TP, n = 23; TP, n = 21) and 139 were categorized as having an ALBI grade 2 (TACE+TP, n = 77; TP, n = 62). The patients' baseline characteristics were comparable among the two groups irrespective of baseline ALBI classification (Table 2).

Table 1 Baseline Characteristics of Patients

Characteristic	Overall (n=183)	TACE+TP (n=100)	TP (n=83*)	P value
Gender				0.148
Male	153 (83.6%)	80 (80.0%)	73 (88.0%)	
Female	30 (16.4%)	20 (20.0%)	10 (12.0%)	
Age (years)	60.0±11.2	60.0±11.0	60.0±11.5	0.981
ECOG PS				0.362
0	108 (59.0%)	56 (56.0%)	52 (62.7%)	
1	75 (41.0%)	44 (44.0%)	31 (37.3%)	
HBV				0.462
Absent	61 (33.3%)	31 (31.0%)	30 (36.1%)	
Present	122 (66.7%)	69 (69.0%)	53 (63.9%)	

(*Continued*)

Table 1 (Continued).

Characteristic	Overall (n=183)	TACE+TP (n=100)	TP (n=83*)	P value
Child-Pugh grade				0.080
A	139 (76.0%)	81 (81.0%)	58 (69.9%)	
B	44 (24.0%)	19 (19.0%)	25 (30.1)	
Tumor size				0.381
≤5 cm	(39.9%)	37 (37.0%)	36 (43.4%)	
>5 cm	110 (60.1%)	63 (63.0%)	47 (56.6.3%)	
Tumor distribution				0.077
Single	33 (18.0%)	25 (25.0%)	12 (14.5%)	
Multiple	150 (82.0%)	75 (75.0%)	71 (85.5%)	
Extrahepatic metastasis				0.075
Absent	74 (40.4%)	48 (48.0%)	29 (34.9%)	
Present	109 (59.6%)	52 (52.0%)	54 (65.1%)	
Vascular invasion				0.686
Absent	83 (45.4%)	44 (44.0%)	39 (47.0%)	
Present	100 (54.6%)	56 (56.0%)	44 (53.0%)	
AFP (ng/dl)				0.448
≤400	120 (65.6%)	68 (68.0%)	52 (62.7%)	
>400	63 (34.4%)	32 (32.0%)	31 (37.3%)	
Pharmacological therapy				0.446
Sorafenib/lenvatinib plus camrelizumab	107 (58.5%)	61 (61.0%)	46 (55.4%)	
Bevacizumab plus sintinimab	76 (41.5%)	39 (39.0%)	37 (44.6%)	
Historical treatment+				0.082
Absent	127 (69.4%)	64 (64.0%)	63 (75.9%)	
Present	56 (30.6%)	36 (36.0%)	20 (24.1%)	

Notes: *Data for patients with ALBI grade 3 were not analyzed because of the small size (n = 5). [+]Historical treatment included curative resection, ablation, and transarterial chemoembolization.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBV, Hepatitis B virus; AFP, alpha-fetoprotein.

Table 2 Baseline Characteristics of Patients According to Baseline ALBI Grade

Characteristics	ALBI Grade 1		P Value	ALBI Grade 2		P Value
	TACE+TP (n=23)	TP (n=21)		TACE+TP (n=77)	TP (n=62)	
Gender			0.102			0.654
Male	15 (65.2%)	19 (90.5%)		65 (84.4%)	54 (87.1%)	
Female	8 (34.8%)	2 (9.5%)		12 (15.6%)	8 (12.9%)	
Age [years]	58.00±9.90	58.95±11.15	0.766	60.65±11.34	60.35±11.65	0.881
EGOG PS			0.837			0.270
0	16 (69.6%)	14 (66.7%)		40 (51.9%)	38 (61.3%)	
1	7 (30.4%)	7 (33.3%)		37 (48.1%)	24 (38.7%)	
HBV			0.460			0.207
Absent	9 (39.1%)	6 (28.6%)		22 (28.6%)	24 (38.7%)	
Present	14 (60.9%)	15 (71.4%)		55 (71.4%)	38 (61.3%)	
Child-Pugh grade			0.201			0.165
A	23 (100%)	18 (85.7%)		58 (75.3%)	40 (64.5%)	
B	0	3 (14.3%)		19 (24.7%)	22 (35.5%)	

(*Continued*)

Table 2 (Continued).

Characteristics	ALBI Grade 1		P Value	ALBI Grade 2		P Value
	TACE+TP (n=23)	TP (n=21)		TACE+TP (n=77)	TP (n=62)	
Tumor size			0.537			0.180
≤5 cm	12 (52.2%)	9 (42.9%)		25 (32.5%)	27 (43.5%)	
>5 cm	11 47.8%)	12 (57.1%)		52 (67.5%)	35 (56.5%)	
Tumor distribution			0.803			0.098
Single	5 (21.7%)	3 (14.3%)		20 (26.0%)	9 (14.5%)	
Multiple	18 (78.3%)	18 (85.7%)		57 (74.0%)	53 (85.5%)	
Extrahepatic metastasis			0.919			0.052
Absent	8 (34.8%)	7 (33.3%)		40 (51.9%)	22 (35.5%)	
Present	15 (65.2%)	14 (66.7%)		37 (48.1%)	40 (64.5%)	
Vascular invasion			0.239			0.852
Absent	8 (34.8%)	11 (52.4%)		36 (46.8%)	28 (45.2%)	
Present	15 (65.2%)	10 (47.6%)		41 (53.2%)	34 (54.8%)	
AFP (ng/dl)			0.820			0.463
≤400	15 (65.2%)	13 (61.9%)		53 (68.8%)	39 (62.9%)	
>400	8 (34.8%)	8 (38.1%)		24 (31.2%)	23 (37.1%)	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBV, Hepatitis B virus; AFP, alpha-fetoprotein.

Time to Progression of ALBI Grade

Overall, the median duration until ALBI grade progression, indicative of liver function deterioration, was comparable between the TACE+TP and TP groups, with no significant difference observed (11.2 vs 19.3 months, P = 0.353) (Figure 2). Comparable findings were noted when evaluating the TACE+TP and TP groups patients initially categorized as ALBI grade 1 (3.5 vs 3.0 months; P = 0.736) and grade 2 (16.6 vs 26.4 months; P = 0.140), which suggested that TACE+TP did not negatively affect liver function than PT.

Change from Treatment Baseline in ALBI Score

In aggregate, change in ALBI scores from baseline to the final assessment did not significantly differ between the TACE +TP and TP groups, with a negligible difference in the least squares mean (0.084; 95% CI −0.092−0.261). Likewise, when the change in baseline ALBI scores was stratified by ALBI classification, the difference between these two groups in the least squares mean was minimal and not significantly different for both ALBI grade 1 (0.016; 95% CI −0.375 −0.406) and ALBI grade 2 (0.112; 95% CI −0.084−0.308), indicating a comparable trend across both treatment arms.

Efficacy by ALBI Grade

There was an improvement in OS with TACE+TP versus TP independent of baseline ALBI grading. For patients classified with an ALBI grade of 1, TACE+TP group had a significantly superior OS than TP group [median, 30.4 (95% CI 21.0–39.7) vs 14.0 (95% CI 10.8–17.2) months, HR = 0.242 (95% CI 0.071–0.826), P = 0.014, Figure 3A]. In the case of ALBI grade 2 patients, TACE+TP group also had a significantly superior OS than TP group [median, 21.7 (95% CI 16.8–26.5) vs 12.0 (95% CI not reach–not reach) months, HR = 0.593 (95% CI 0.357–0.985), P = 0.041, Figure 3B]. Consistent with the findings for OS, TACE+TP demonstrated a trend toward enhanced PFS across all ALBI grade categories. For patients classified with an ALBI grade of 1, TACE+TP group had a relatively superior PFS trend than TP group [median, 20.0 (95% CI 5.3–34.6) vs 7.8 (95% CI 2.8–12.8) months, HR = 0.602 (95% CI 0.259–1.402), P = 0.234, Figure 4A]. In the case of ALBI grade 2 patients, TACE+TP group also had a relatively superior PFS trend than TP group [median, 13.4 (95% CI 11.2–15.6) vs 9.4 (95% CI 6.4–12.5) months, HR = 0.785 (95% CI 0.499–1.235), P = 0.293, Figure 4B]. In addition, no instances of therapy-related mortality or unexpected serious adverse effects were reported in our study.

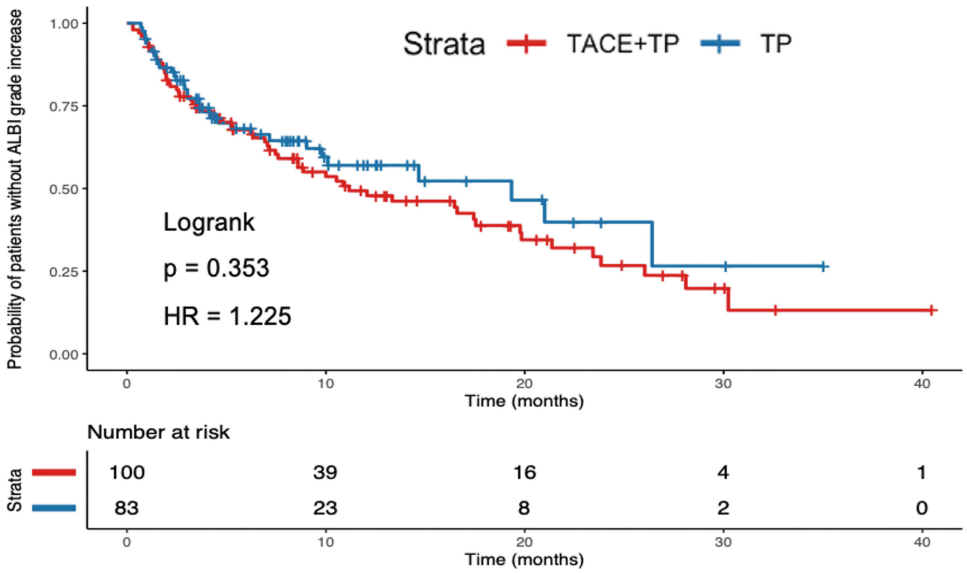

Figure 2 Kaplan–Meier estimates of time to ALBI grade increase stratified by the group.
Abbreviation: ALBI, albumin-bilirubin.

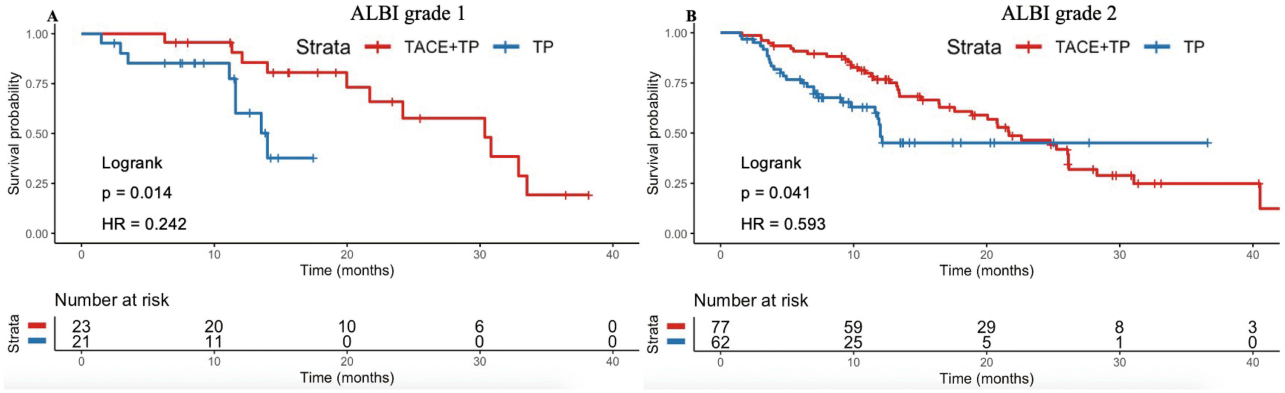

Figure 3 Kaplan–Meier estimates of overall survival by (**A**) ALBI grade 1 and (**B**) ALBI grade 2.
Abbreviation: ALBI, albumin-bilirubin.

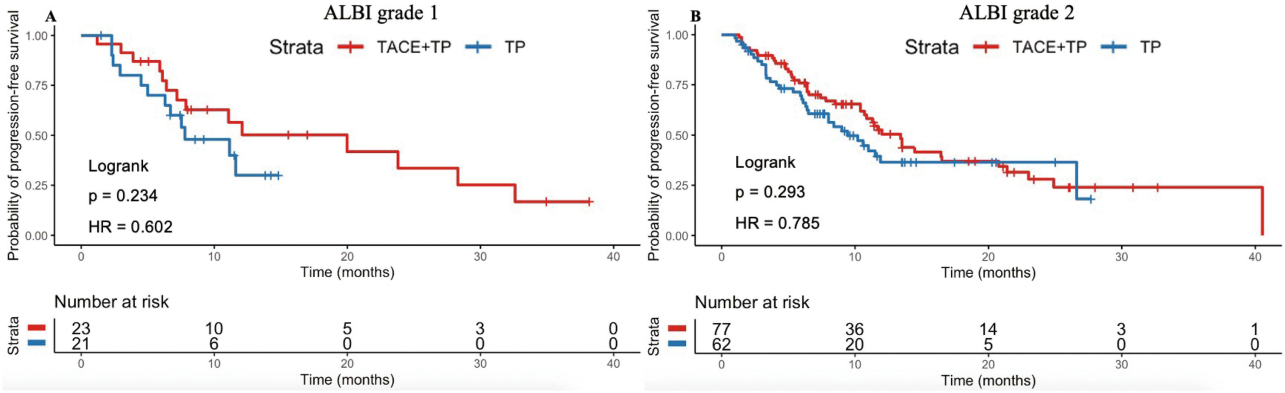

Figure 4 Kaplan–Meier estimates of progression-free survival by (**A**) ALBI grade 1 and (**B**) ALBI grade 2.
Abbreviation: ALBI, albumin-bilirubin.

Discussion

In our study, we observed that time to progression of the ALBI grade and change in ALBI score between the initial baseline and the final measurement were comparable between the TACE+TP and TP groups, irrespective of the initial ALBI grade. Furthermore, TACE+TP demonstrated a significant enhancement in OS and a consistent trend toward improved PFS across both ALBI grade 1 and grade 2 subgroups when compared to TP.

The worsening of liver function in HCC patients restricts available treatment options and adversely affects their prognosis, highlighting the critical importance of liver function in managing the disease.[23] TACE is an established therapeutic standard that has been employed for unresectable HCC over numerous years, reflecting its enduring role in oncology. Although TACE could contribute to a decrease in liver function,[24] a study has demonstrated that the clinical benefits and safety of CP B (score 7) HCC patients who underwent TACE were comparable to those of CP-A patients.[25] Recently, debates have emerged regarding the optimal therapeutic strategy for HCC when liver resection and radiofrequency ablation are not viable options, specifically concerning whether to prioritize TACE or systemic therapy approaches.[26–28] For enhanced prioritization of therapeutic options, the ALBI classification has been recognized as a valuable criterion for evaluating liver function. In instances where TACE fails to elicit a complete response after a single session, it is advisable to contemplate the early integration of systemic therapy prior to re-initiating TACE.

Interestingly, TACE+PT did not adversely influence liver function than PT in HCC patients, which was determined by monitoring time to progression in ALBI grade and observing changes in ALBI scores. The potential reasons might be explained as follows: 1) all patients underwent super-selective TACE, which minimally impaired liver function; and 2) TACE+PT improved clinical efficacy in advanced HCC while reducing the number of repeated TACE.

Previous research assessing the influence of baseline ALBI grading on treatment efficacy in advanced HCC has yielded results that are largely in alignment with our study's observations. Specifically, in the context of first-line therapy, a post-hoc analysis from the phase III REFLECT trial demonstrated that patients undergoing lenvatinib experienced more favorable clinical benefits (OS and PFS) versus those treated with sorafenib, across all ALBI grade categories.[18] Furthermore, in the second-line therapy context, a post-hoc analysis of the REACH plus REACH-2 trials revealed superior survival outcomes (OS and PFS) with ramucirumab versus placebo, irrespective of the patients' baseline ALBI classification.[29] A consistent finding was revealed in patients receiving cabozantinib.[30] Meanwhile, a post-hoc analysis of the KEYNOTE-240 study, evaluating pembrolizumab against placebo after sorafenib as a second-line treatment, indicated a trend toward enhanced OS and PFS with pembrolizumab than placebo, irrespective of the patients' baseline ALBI grade.[31] Within the scope of our study, we observed a significant improvement in OS and a noteworthy trend toward enhanced PFS among patients receiving TACE+TP, as compared to those receiving TP alone, across all baseline ALBI grading categories.

Furthermore, HCC patients with a baseline ALBI grade of 1 exhibited more favorable survival benefits versus patients with an ALBI grade of 2 or higher, following treatment with sorafenib[32] and ramucirumab.[29] The ALBI grade had demonstrated prognostic significance for treatment outcomes in HCC patients, irrespective of whether they received atezolizumab plus bevacizumab or sorafenib alone.[19] These findings underscored the critical importance of preserving liver function to maximize the therapeutic benefits derived by patients undergoing TACE+TP.

The study's findings should be interpreted with consideration of several inherent limitations. First, the retrospective design might predispose the research to potential biases, underscoring the need for caution in extrapolating these results. Prospective studies would offer a more robust framework for validation. Second, the limited sample size of patients with a baseline ALBI grade of 3 precluded a comprehensive analysis of outcomes for this subgroup. Finally, the analysis employed the ALBI grading system, prioritizing its objectivity over the CP grading system. Unlike the CP system, the ALBI grade did not encompass subjective evaluations of clinical signs, thereby providing a more reliable measure of liver function.

Conclusions

TACE+PT did not negatively affect liver function compared to PT in HCC patients, as indicated by the changes in ALBI scores, while a significant improvement in OS and a promising trend toward enhanced PFS with TACE+PT were observed in both ALBI grade groups.

Author Contributions

Jingyu Qian and Wen-Bin Ding contributed as corresponding authors.

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Cancer Interventional Research Fund of China Health Promotion Foundation (NO. XM_2018_011_0006_01), the second phase of interventional medicine research project of Jiangsu Medical Association [NO. SYH-3201140-0047(2022004)] and the Nantong City Health Commission's scientific research Project (No. MS2022019).

Disclosure

No potential conflicts of interest were disclosed.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin*. 2021;71(1):7–33. doi:10.3322/caac.21654
2. Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. *Nat Rev Dis Primers*. 2021;7(1):6. doi:10.1038/s41572-020-00240-3
3. Park JW, Chen M, Colombo M, et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. *Liver Int*. 2015;35(9):2155–2166. doi:10.1111/liv.12818
4. Villanueva A. Hepatocellular carcinoma. *N Engl J Med*. 2019;380(15):1450–1462. doi:10.1056/NEJMra1713263
5. European Association for the Study of the Liver. Electronic address eee, European Association for the study of the L. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2018;69(1):182–236. doi:10.1016/j.jhep.2018.03.019
6. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology*. 2018;67(1):358–380. doi:10.1002/hep.29086
7. Zhou J, Sun H, Wang Z, et al. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (2019 Edition). *Liver Cancer*. 2020;9(6):682–720. doi:10.1159/000509424
8. Zhu HD, Li HL, Huang MS, et al. Transarterial chemoembolization with PD-(L)1 inhibitors plus molecular targeted therapies for hepatocellular carcinoma (CHANCE001). *Signal Transduct Target Ther*. 2023;8(1):58. doi:10.1038/s41392-022-01235-0
9. Lencioni R, Kudo M, Erinjeri J, et al. EMERALD-1: a Phase 3, randomized, placebo-controlled study of transarterial chemoembolization combined with durvalumab with or without bevacizumab in participants with unresectable hepatocellular carcinoma eligible for embolization. *Journal of Clinical Oncology*. 2024;42(3_suppl):LBA432–LBA432. [ASCO GI. LBA432]. doi:10.1200/JCO.2024.42.3_suppl.LBA432
10. Cai M, Huang W, Liang W, et al. Lenvatinib, sintilimab plus transarterial chemoembolization for advanced stage hepatocellular carcinoma: a phase II study. *Liver Int*. 2024;44(4):920–930. doi:10.1111/liv.15831
11. Pan Y, Zhu X, Liu J, et al. Systemic therapy with or without transcatheter intra-arterial therapies for unresectable hepatocellular carcinoma: a real-world, multi-center study. *Front Immunol*. 2023;14:1138355. doi:10.3389/fimmu.2023.1138355
12. Huang JT, Zhong BY, Jiang N, et al. Transarterial chemoembolization combined with immune checkpoint inhibitors plus tyrosine kinase inhibitors versus immune checkpoint inhibitors plus tyrosine kinase inhibitors for advanced hepatocellular carcinoma. *J Hepatocell Carcinoma*. 2022;9:1217–1228. doi:10.2147/JHC.S386672
13. Jin ZC, Chen JJ, Zhu XL, et al. Immune checkpoint inhibitors and anti-vascular endothelial growth factor antibody/tyrosine kinase inhibitors with or without transarterial chemoembolization as first-line treatment for advanced hepatocellular carcinoma (CHANCE2201): a target trial emulation study. *EClinMed*. 2024;72:102622. doi:10.1016/j.eclinm.2024.102622
14. Raoul JL, Bruix J, Greten TF, et al. Relationship between baseline hepatic status and outcome, and effect of sorafenib on liver function: SHARP trial subanalyses. *J Hepatol*. 2012;56(5):1080–1088. doi:10.1016/j.jhep.2011.12.009
15. Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-The ALBI grade. *J Clin Oncol*. 2015;33(6):550–558. doi:10.1200/JCO.2014.57.9151
16. Cho WR, Hung CH, Chen CH, et al. Ability of the post-operative ALBI grade to predict the outcomes of hepatocellular carcinoma after curative surgery. *Sci Rep*. 2020;10(1):7290. doi:10.1038/s41598-020-64354-0
17. Abdel-Rahman O. Impact of baseline characteristics on outcomes of advanced HCC patients treated with sorafenib: a secondary analysis of a phase III study. *J Cancer Res Clin Oncol*. 2018;144(5):901–908. doi:10.1007/s00432-018-2610-z

18. Vogel A, Frenette C, Sung M, et al. Baseline liver function and subsequent outcomes in the phase 3 reflect study of patients with unresectable hepatocellular carcinoma. *Liver Cancer*. 2021;10(5):510–521. doi:10.1159/000516490
19. Kudo M, Finn RS, Cheng AL, et al. Albumin-bilirubin grade analyses of atezolizumab plus bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma: a post hoc analysis of the phase III IMbrave150 study. *Liver Cancer*. 2023;12(5):479–493. doi:10.1159/000529996
20. Hiraoka A, Michitaka K, Kumada T, et al. Validation and potential of albumin-bilirubin grade and prognostication in a nationwide survey of 46,681 hepatocellular carcinoma patients in Japan: the need for a more detailed evaluation of hepatic function. *Liver Cancer*. 2017;6(4):325–336. doi:10.1159/000479984
21. Zhong BY, Yan ZP, Sun JH, et al. Prognostic performance of albumin-bilirubin grade with artificial intelligence for hepatocellular carcinoma treated with transarterial chemoembolization combined with sorafenib. *Front Oncol*. 2020;10:525461. doi:10.3389/fonc.2020.525461
22. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis*. 2010;30(1):52–60. doi:10.1055/s-0030-1247132
23. Ren M, Li J, Xue R, Wang Z, Coll SL, Meng Q. Liver function and energy metabolism in hepatocellular carcinoma developed in patients with hepatitis B-related cirrhosis. *Medicine*. 2019;98(19):e15528. doi:10.1097/MD.0000000000015528
24. Hiraoka A, Kumada T, Kudo M, et al. Hepatic function during repeated TACE procedures and prognosis after introducing sorafenib in patients with unresectable hepatocellular carcinoma: multicenter analysis. *Dig Dis*. 2017;35(6):602–610. doi:10.1159/000480256
25. Jiang JQ, Huang JT, Zhong BY, et al. Transarterial chemoembolization for patients with unresectable hepatocellular carcinoma with Child-Pugh B7. *J Hepatocell Carcinoma*. 2023;10:1629–1638. doi:10.2147/JHC.S422300
26. Tamaki N, Tada T, Kurosaki M, et al. Optimal threshold of alpha-fetoprotein response in patients with unresectable hepatocellular carcinoma treated with atezolizumab and bevacizumab. *Invest New Drugs*. 2022;40(6):1290–1297. doi:10.1007/s10637-022-01303-w
27. Kuroda H, Oikawa T, Ninomiya M, et al. Objective response by mRECIST to initial lenvatinib therapy is an independent factor contributing to deep response in hepatocellular carcinoma treated with lenvatinib-transcatheter arterial chemoembolization sequential therapy. *Liver Cancer*. 2022;11(4):383–396. doi:10.1159/000522424
28. Kondo Y, Morosawa T, Minami S, Tanaka Y. DEB-TACE combined with hepatic artery infusion chemotherapy might be an affordable treatment option for advanced stage of HCC. *Sci Rep*. 2022;12(1):16868. doi:10.1038/s41598-022-21472-1
29. Kudo M, Galle PR, Brandi G, et al. Effect of ramucirumab on ALBI grade in patients with advanced HCC: results from REACH and REACH-2. *JHEP Rep*. 2021;3(2):100215. doi:10.1016/j.jhepr.2020.100215
30. Kelley RK, Miksad R, Cicin I, et al. Efficacy and safety of cabozantinib for patients with advanced hepatocellular carcinoma based on albumin-bilirubin grade. *Br J Cancer*. 2022;126(4):569–575. doi:10.1038/s41416-021-01532-5
31. Vogel A, Merle P, Verslype C, et al. ALBI score and outcomes in patients with hepatocellular carcinoma: post hoc analysis of the randomized controlled trial KEYNOTE-240. *Ther Adv Med Oncol*. 2021;13:17588359211039928. doi:10.1177/17588359211039928
32. Kuo YH, Wang JH, Hung CH, et al. Albumin-Bilirubin grade predicts prognosis of HCC patients with sorafenib use. *J Gastroenterol Hepatol*. 2017;32(12):1975–1981. doi:10.1111/jgh.13783