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ORIGINAL ARTICLE

Retrospective Study

Lenvatinib, sintilimab combined interventional treatment *vs* bevacizumab, sintilimab combined interventional treatment for intermediate-advanced unresectable hepatocellular carcinoma

Ru-Yu Han, Lei-Juan Gan, Meng-Ran Lang, Shao-Hua Ren, Dong-Ming Liu, Guang-Tao Li, Ya-Yue Liu, Xin-Di Tian, Kang-Wei Zhu, Li-Yu Sun, Lu Chen, Tian-Qiang Song

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Abstract

BACKGROUND

Bevacizumab and sintilimab combined interventional treatment (BeSiIT) and L envatinib and sintilimab combined interventional treatment (LeSiIT) are two commonly used therapeutic regimens for intermediate-advanced hepatocellular carcinoma (HCC) in clinical practice.

AIM

To compare the clinical efficacy and safety of BeSiIT and LeSiIT for the treatment of intermediate and advanced HCC.

METHODS

Patients diagnosed with intermediate-advanced HCC and initially treated with

BeSiIT or LeSiIT in the Tianjin Medical University Cancer Institute and Hospital between February 2020 and July 2021 were included. The primary endpoint was progression-free survival (PFS), and the secondary endpoints were overall survival (OS), objective response rate (ORR), disease control rate (DCR), conversion rate, and treatment-related adverse events.

RESULTS

Total 127 patients met the inclusion criteria and were divided into BeSiIT and LeSiIT groups. Twenty-eight and fifty patients in the BeSiIT and LeSiIT groups, respectively, were assessed after 1:2 propensity score matching. PFS and OS rates were not significantly different between the two groups. No significant variations were noted in ORRs or DCRs according to the Response Evaluation Criteria in Solid Tumors (RECIST), and modified RECIST. BeSiIT group showed a better conversion rate than the LeSiIT group (P = 0.043). Both groups showed manageable toxicity profiles. Multivariate analysis showed that the independent factors associated with PFS were alpha-fetoprotein levels and carcinoembryonic antigen score.

CONCLUSION

In intermediate-to-advanced HCC, the BeSiIT and LeSiIT groups exhibited acceptable toxicities and comparable PFS, OS, and ORR.

Key Words: Hepatocellular carcinoma; Molecular targeted therapy; Immunotherapy; Interventional treatment; Propensity score matching

Core Tip: In this study, we compared the efficacy and safety of two treatments [bevacizumab plus sintilimab plus interventional treatment (BeSiIT) and lenvatinib plus sintilimab plus interventional treatment (LeSiIT)] in intermediate to advanced hepatocellular carcinoma (HCC). In this study, we found that the triple combination of BeSiIT and LeSiIT improved the prognosis of intermediate- and advanced-stage HCC, with comparable efficacy and acceptable toxicity for both treatments. And a novel marker was identified: Alpha-fetoprotein and carcinoembryonic antigen score. It was shown to be an independent prognostic factor associated with progression-free survival in multivariate analysis.

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INTRODUCTION

Liver cancer is a global health challenge, and its incidence is continually increasing[1,2]. China bears a disproportionate share of liver cancer cases, with hepatocellular carcinoma (HCC) representing the majority of cases[3-5]. Potentially curative treatments such as ablation, resection, and liver transplantation have been considered for early stage HCC[6]. However, nearly 64% of Chinese patients with HCC are initially diagnosed at moderate or advanced stages [Barcelona Clinic Liver Cancer (BCLC) stages B and C] when surgical resection is typically contraindicated[7-9].

Notable progress in non-surgical treatments for HCC has been achieved recently. Systemic therapy, particularly the combination of molecular targeted therapy and immunotherapy, has shown promising results in achieving an objective response rate (ORR) of approximately 30% and enhancing the survival outcomes in patients with intermediate-to-advanced unresectable HCC[10,11]. Lenvatinib, a tyrosine kinase inhibitor (TKI), was reported to be not inferior to sorafenib in the phase III REFLECT trial[12,13] and has become the first-line systemic therapy for the treatment of advanced HCC. Immune checkpoint inhibitors, including programmed death-1 (PD-1) and programmed death ligand 1 inhibitors, can reverse T-cell suppression and have demonstrated promising clinical efficacy and safety in advanced HCC patients[14-16]. Bevacizumab is a recombinant humanized monoclonal antibody that effectively blocks angiogenic signaling pathway, thereby inhibiting tumor neovascularization and tumor cell growth. The phase 2-3 ORIENT-32 study showed that the combination of sintilimab, a PD-1 inhibitor, and bevacizumab, a vascular endothelial growth factor (VEGF) antibody, significantly improved the overall survival (OS) and progression-free survival (PFS) in Chinese patients with advanced HCC[17]. Therefore, sintilimab plus bevacizumab has become the first-line treatment for advanced HCC in China. Recently, interest in the combined use of interventional therapy and targeted-immunotherapy has been growing [18-21].

Owing to their distinct anticancer mechanisms, a combination of molecular targeted therapies, PD-1 inhibitors, and interventional procedures has shown promising effectiveness in treating intermediate to advanced HCC[22-25]. However, comparative studies evaluating the efficacy of combined bevacizumab and sintilimab with interventional therapy (BeSiIT)

vs lenvatinib and sintilimab with interventional therapy (LeSiIT) for treating HCC are lacking. Therefore, in this retrospective study, we used propensity score matching (PSM) to compare the efficacies and safety of BeSiIT and LeSiIT, aiming to provide a reference for the treatment of intermediate-advanced HCC.

MATERIALS AND METHODS

Patients

This retrospective study was conducted according to the Declaration of Helsinki (revised in 2013) and was approved by the ethics committee of Tianjin Medical University Cancer Institute and Hospital. The requirement for informed consent was waived. This study complied with the Good Clinical Practice guidelines and applicable local laws. Any patient data that could identify individual patients were anonymized and de-identified before analysis.

Medical records of patients diagnosed with intermediate-advanced HCC who were treated with BeSiIT and LeSiIT at the Department of Hepatobiliary Oncology of Tianjin Medical University Cancer Institute and Hospital between February 2020 and July 2021 were reviewed for eligibility. The inclusion criteria were as follows: (1) Age 18 years or older; (2) Received first-line treatment of BeSiIT or LeSiIT; (3) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1; (4) BCLC stage B or C; (5) Child-Pugh (CP) class A or B; (6) At least one measurable intrahepatic lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; (7) At least two cycles of BeSiIT or LeSiIT; and (8) Optimal organ function (absolute neutrophil count of ≥ 1.2 × 10^9/L, platelet count of ≥ 60 × 10^9/L, albumin concentration of ≥ 30 g/L, total bilirubin concentration of < 30 μmol/L, aspartate and alanine transaminase ≤ 5 × upper limit of the normal range, creatinine clearance rate of ≤ 1.5 × upper limit of the normal range, and left ventricular ejection ≥ 45%). The exclusion criteria were as follows: CP class C, unmeasurable intrahepatic lesion, presence of tumors other than HCC, incomplete medical information, and loss to follow-up.

Treatments

The patients in the BeSiIT group received 200 mg of sintilimab (Daboshu®, Innovent, Suzhou, China; 200 mg q3w) intravenously for 60 minutes, followed by 15 mg/kg of body weight of bevacizumab (BYVASDA®, Innovent, China; 15 mg/kg q3w) intravenously for 90 minutes (second infusion for 60 minutes and 30 minutes afterward if no infusion reaction occurred) every 3 weeks.

In the LeSiIT group, lenvatinib (Levima®, Eisai, Tokyo, Japan; 8 mg qd) was taken orally, while sintilimab (Daboshu®, Innovent, Suzhou, China; 200 mg q3w) was administered intravenously at a dose of 200 mg every 3 weeks. The first administration of sintilimab occurred within 7 days of lenvatinib treatment initiation.

Interventions were performed during every treatment cycle by two senior interventional physicians (Xing WG and Liu F). The intervention protocol was decided by the interventionalists.

In TACE treatments, the tip of the catheter is inserted into the artery branches for tumor feeding according to the tumor size, location, and arterial supply. Embolization was initially performed using microspheres of different diameters or drug-eluting beads. The trunk was subsequently embolized with an absorbable gelatine sponge until the bleeding stopped. Pharmorubicin was administered for chemotherapy.

For HAIC treatments, the 5-fluoro-uracil, leucovorin, and oxaliplatin regimen was administered *via* the hepatic artery as follows: 85 or 135 mg/m^2 oxaliplatin, 400 mg/m^2 leucovorin, and 400 mg/m^2 fluorouracil on the first day and 2400 mg/m^2 fluorouracil for 46 hours.

The patients received sintilimab and bevacizumab/lenvatinib within 3 days before or after the initiation of HAIC/TACE. Treatment was discontinued in cases of disease progression, conversion therapy necessitated by tumor shrinkage, intolerable toxicity, patient withdrawal of consent, or alterations in the treatment regimen.

In patients who met the conversion criteria, bevacizumab was withheld for 4-6 weeks prior to surgery, lenvatinib for 1-2 weeks, and sintilimab for 1-3 weeks. Postoperative medication was discontinued 2-4 weeks before resumption.

Data collection and study objectives

We collected and analyzed a comprehensive set of laboratory and radiological data, including demographic information such as age and sex, as well as clinical parameters such as the presence of hepatitis, liver cirrhosis, tumor characteristics, CP classification, BCLC stage, ECOG PS, extrahepatic metastasis, vascular invasion, and alpha-fetoprotein (AFP) levels. Laboratory data were obtained within 3 days before treatment initiation, whereas imaging evaluations, consisting of contrast-enhanced magnetic resonance imaging or computed tomography scans, were conducted within 7 days before treatment initiation and subsequently every 2 to 3 months. All imaging data were independently assessed by two radiologists. If there was a disagreement, another experienced radiologist made the final decision.

The primary endpoint of the study was PFS, defined as the time from the start of treatment to disease progression or death, whichever came first, according to the RECIST criteria. The secondary endpoints included OS, ORR, disease control rate (DCR), and treatment-related adverse events (TRAEs). OS was defined as the time from the start of treatment to death from any cause. ORR was defined as the proportion of patients with a complete response (CR) or partial response (PR) that was maintained for at least 4 weeks after the first radiological confirmation. The DCR was defined as the proportion of patients with ORR and stable disease. ORR and DCR were evaluated using both RECIST version 1.1 and modified RECIST (mRECIST)[26,27]. TRAEs were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Statistical analysis

All the baseline categorical data were analyzed using Pearson's χ^2 test or Fisher's exact test. The Kaplan-Meier method was used for survival analysis, and survival curves were compared using the log-rank test. Cox regression analysis was performed to analyze the clinical characteristics of the two cohorts using PFS as the outcome variable. Statistically significant variables in the univariate analysis were included in the multivariate Cox regression analysis. Hazard ratios (HR) and 95%CI were determined. Statistical significance was denoted by two-tailed *P* values of < 0.05. All data analyses were performed using SPSS version 26.0 (SPSS, Chicago, IL, United States) and R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). In addition, the X-tile software was used to determine the optimal cutoff values for serum AFP and carcinoembryonic antigen (CEA) levels based on PFS (the normal upper limits of AFP and CEA in our hospital were 7.00 ng/mL and 5.00 ng/mL). The patients were divided into low-level (score = 0) and high-level (score = 1) groups according to their X-tile results. The α-fetoprotein and carcinoembryonic antigen score (AFCE) of each patient was defined as the sum of the AFP and CEA scores. All patients were subdivided into groups of 0, 1, or 2 based on their AFCE score.

RESULTS

Demographic characteristics

A total of 208 patients diagnosed with intermediate-to-advanced HCC and treated with either BeSiIT or LeSiIT were screened between February 2020 and July 2021. Among them, 81 patients were excluded based on predetermined inclusion and exclusion criteria, including 8 with a CP classification of C, 5 with unmeasurable intrahepatic lesions, 4 with other malignant tumors besides HCC, 26 with incomplete medical records, and 38 who were lost to follow-up. Ultimately, 127 patients were included in the study, 32 of whom received BeSiIT, and 95 who received LeSiIT. PSM was used to reduce confounding[28]. After PSM, the BeSiIT and LeSiIT groups comprised 28 and 50 patients, respectively (Figure 1). The medium follow-up duration was 13.0 months (95%CI: 12.0-15.0) (reverse Kaplan-Meier method).

The baseline characteristics of the patients are summarized in Table 1. The tumor number and vascular invasion were significantly different between the two groups. No differences were observed after PSM, indicating that the laboratory and radiological data of the two groups were equally distributed. Most patients were lesser than 65 years in age (75.0% and 70.0% in the BeSiIT and LeSiIT groups, respectively). The study population was predominantly male (85.7% and 82.0% for the BeSiIT and LeSiIT groups, respectively). Most patients had hepatitis B virus infections (89.3% and 92.0% in the BeSiIT and LeSiIT groups, respectively) and received antiviral therapy. Most patients in the BeSiIT and LeSiIT groups had cirrhosis (71.4% and 72.0%, respectively) and their AFP concentrations were less than 400 ng/mL (53.6% and 56.0% in the BeSiIT and LeSiIT groups, respectively). The tumor sizes of most patients were less than or equal to 10 cm (60.7% and 68.0% for the BeSiIT and LeSiIT groups, respectively), and the majority had 3 or fewer tumors (71.4% and 68.0% for the BeSiIT and LeSiIT groups, respectively). Most patients were classified as CP class A (82.1% and 80.0% in the BeSiIT and LeSiIT groups, respectively), BCLC stage C (75.0% and 72.0% in the BeSiIT and LeSiIT groups, respectively), and ECOG performance status 0 (78.6% and 72.0% in the BeSiIT and LeSiIT groups, respectively). Most patients did not have metastasis (67.9% and 68.0% for the BeSiIT and LeSiIT groups, respectively), but most had vascular invasion (64.3% and 52.0% for the BeSiIT and LeSiIT groups, respectively).

Sixteen patients underwent conversion therapy, including surgical resection or radiofrequency ablation, in the BeSiIT group, and 13 underwent conversion therapy in the LeSiIT group. The conversion therapy rates in the two cohorts were significantly different ($P = 0.043$).

Survival

Before PSM, 18 patients showed disease progression and 10 died at the time of analysis in the BeSiIT group, while 45 patients showed disease progression and 27 died in the LeSiIT group. The median PFS (mPFS) was 11.0 months [95%CI: 6.0-not available (NA)] for the BeSiIT group, compared with 12.0 months (95%CI: 9.0-NA) for the LeSiIT group. The OS of the patients in both groups were less than the median OS (mOS) (BeSiIT, 95%CI: NA-NA; LeSiIT, 95%CI: 15.0-NA; Figure 2A and B). After PSM, 16 patients showed disease progression and 10 patients died at the time of analysis in the BeSiIT group; 23 patients showed disease progression and 17 patients died in the LeSiIT group. The mPFS was 11.0 months (95%CI: 6.0-NA) in the BeSiIT group compared to 12.0 months (95%CI: 7.0-NA) in the LeSiIT group. The mOS (95%CI: 13.0-NA) could not be calculated in the BeSiIT group, while the mOS was 16 months in the LeSiIT group (95%CI: 13.0-NA) (Figure 2C and D). No statistically significant differences were noted between the PFS and OS among both groups before and after PSM.

A forest plot of the factors associated with PFS and OS is shown in Figure 3. Compared with the BeSiIT group, the LeSiIT group did not demonstrate survival benefits. This indicates that intermediate-to-advanced HCC patients treated with BeSiIT and LeSiIT may have equal survival benefits in these two groups.

ORR

The best tumor responses are listed in Table 2. No significant differences in ORR or DCR were observed between the BeSiIT and LeSiIT groups based on the RECIST criteria (60.7% *vs* 46.0%, $P = 0.791$ and 78.6% *vs* 60.6%, $P = 0.095$, respectively). Moreover, no significant differences were noted between both groups based on the mRECIST criteria (60.7% *vs* 58.0%, $P = 0.815$ and 78.6% *vs* 68.0%, $P = 0.320$, respectively). A waterfall plot was created to show how the intrahepatic target lesion sizes changed in the BeSiIT and LeSiIT groups based on the mRECIST criteria (Figure 4).

Table 1 Baseline characteristics of the bevacizumab plus sintilimab plus interventional treatment and lenvatinib plus sintilimab plus interventional treatment groups before and after propensity score matching, *n* (%)

Variable	Before PSM			After PSM		
	BeSilT (*n* = 32)	LeSilT (*n* = 95)	*P* value	BeSilT (*n* = 28)	LeSilT (*n* = 50)	*P* value
Age			1.000			0.835
< 65 years	24 (75.0)	70 (73.7)		21 (75.0)	35 (70.0)	
≥ 65 years	8 (25.0)	25 (26.3)		7 (25.0)	15 (30.0)	
Sex			0.663			0.916
Female	4 (12.5)	17 (17.9)		4 (14.3)	9 (18.0)	
Male	28 (87.5)	78 (82.1)		24 (85.7)	41 (82.0)	
Hepatitis			0.212			1.000
No	4 (12.5)	4 (4.2)		3 (10.7)	4 (8.0)	
Yes	28 (87.5)	91 (95.8)		25 (89.3)	46 (92.0)	
Liver cirrhosis			1.000			1.000
No	9 (28.1)	27 (28.4)		8 (28.6)	14 (28.0)	
Yes	23 (71.9)	68 (71.6)		20 (71.4)	36 (72.0)	
AFP, ng/mL			1.000			1.000
≤ 400	18 (56.2)	52 (54.7)		15 (53.6)	28 (56.0)	
> 400	14 (43.8)	43 (45.3)		13 (46.4)	22 (44.0)	
Tumor size, cm			0.532			0.689
≤ 10	20 (62.5)	67 (70.5)		17 (60.7)	34 (68.0)	
> 10	12 (37.5)	28 (29.5)		11 (39.3)	16 (32.0)	
Tumor number			0.021[a]			0.953
≤ 3	24 (75.0)	47 (49.5)		20 (71.4)	34 (68.0)	
> 3	8 (25.0)	48 (50.5)		8 (28.6)	16 (32.0)	
Child-Pugh			0.880			1.000
A	26 (81.2)	74 (77.9)		23 (82.1)	40 (80.0)	
B	6 (18.8)	21 (22.1)		5 (17.9)	10 (20.0)	
BCLC stage			0.130			0.984
B	8 (25.0)	40 (42.1)		7 (25.0)	14 (28.0)	
C	24 (75.0)	55 (57.9)		21 (75.0)	36 (72.0)	
ECOG PS			0.136			0.673
0	26 (81.2)	59 (62.1)		22 (78.6)	36 (72.0)	
1	5 (15.6)	31 (32.6)		5 (17.9)	13 (26.0)	
2	1 (3.1)	5 (5.3)		1 (3.6)	1 (2.0)	
Metastasis			0.327			1.000
No	20 (62.5)	70 (73.7)		19 (67.9)	34 (68.0)	
Yes	12 (37.5)	25 (26.3)		9 (32.1)	16 (32.0)	
Vascular invasion			0.027[a]			0.417
No	12 (37.5)	59 (62.1)		10 (35.7)	24 (48.0)	
Yes	20 (62.5)	36 (37.9)		18 (64.3)	26 (52.0)	

[a]*P* value < 0.05, and it is statistically significant.

PSM: Propensity score matching; BeSiIT: Bevacizumab plus sintilimab plus interventional treatment; LeSiIT: Lenvatinib plus sintilimab plus interventional treatment; AFP: A-fetoprotein; BCLC: The Barcelona Clinic Liver Cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status.

Table 2 Summary of the best responses, *n* (%)

Variable	RECIST 11			mRECIST		
	BeSiIT (*n* = 28)	LeSiIT (*n* = 50)	*P* value	BeSiIT (*n* = 28)	LeSiIT (*n* = 50)	*P* value
CR	0 (0.0)	0 (0.0)	-	8 (28.6)	4 (8.0)	0.016[a]
PR	17 (60.7)	23 (46.0)	0.212	9 (32.1)	25 (50.0)	0.127
SD	5 (17.9)	7 (14.0)	0.651	5 (17.9)	5 (1.0)	0.319
PD	6 (21.4)	20 (40.0)	0.095	6 (21.4)	16 (32.0)	0.320
ORR	17 (60.7)	23 (46.0)	0.791	17 (60.7)	29 (58.0)	0.815
DCR	22 (78.6)	30 (60.0)	0.095	22 (78.6)	34 (68.0)	0.320

[a]*P* value < 0.05, and it is statistically significant.
RECIST: Response Evaluation Criteria in Solid Tumors; mRECIST: Modified Response Evaluation Criteria in Solid Tumors; BeSiIT: Bevacizumab plus sintilimab plus interventional treatment; LeSiIT: Lenvatinib plus sintilimab plus interventional treatment; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; ORR: Objective response rate; DCR: Disease control rate.

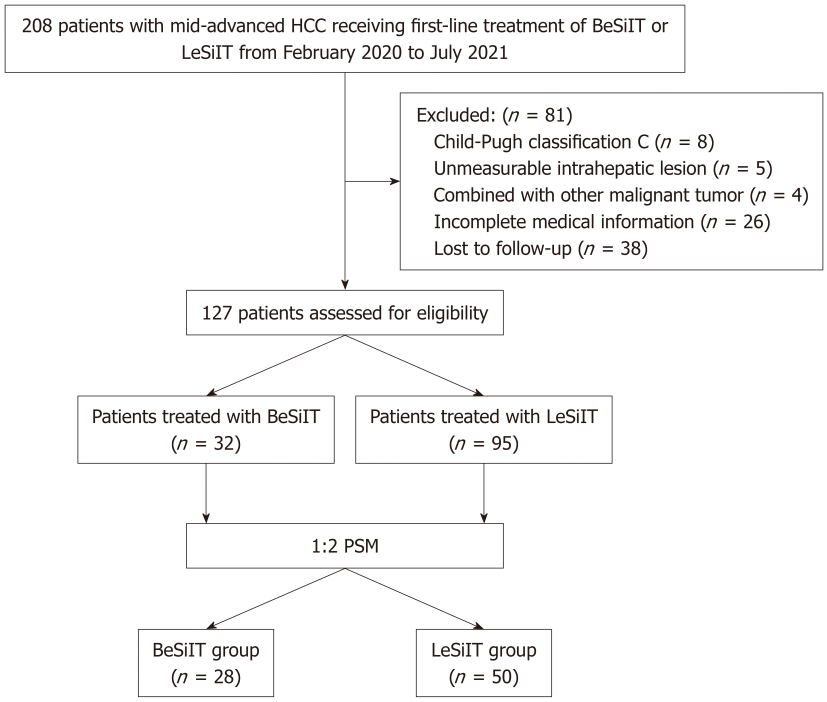

Figure 1 Flowchart for patient selection. HCC: Hepatocellular carcinoma; BeSiIT: Bevacizumab plus sintilimab plus interventional treatment; LeSiIT: Lenvatinib plus sintilimab plus interventional treatment; PSM: Propensity score matching.

Conversion rate

Conversion therapy was performed in 13 patients in the LeSiIT group, with a conversion rate of 26.0%. Sixteen patients in the BeSiIT group received conversion therapy, with a conversion rate of 57.1%. In the LeSiIT group, 11 patients underwent R0 resection and 2 patients received radiofrequency ablation. In the BeSiIT group, 13 patients underwent R0 excision and three patients underwent radiofrequency ablation.

Safety

No treatment-related deaths occurred during the study period. The TRAEs are listed in Table 3. The following TRAEs were more frequent in the LeSiIT group than in the BeSiIT group: Nausea [10 (20.0%) *vs* 0, *P* = 0.018], decreased appetite [12 (24.0%) *vs* 1 (3.6%), *P* = 0.033], diarrhea [10 (20.0%) *vs* 0, *P* = 0.018], fatigue [16 (32.0%) *vs* 2 (7.1%), *P* = 0.027], and

Table 3 A summary of adverse reactions in the bevacizumab plus sintilimab plus interventional treatment and lenvatinib plus sintilimab plus interventional treatment groups, *n* (%)

Variable	BeSiIT (*n* = 28)		LeSiIT (*n* = 50)		*P* value	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Thrombocytopenia	8 (28.5)	2 (7.1)	9 (18.0)	0 (0.0)	0.335	0.059
Neutropenia	4 (14.3)	0 (0.0)	9 (18.0)	1 (2.0)	0.699	0.454
Hypertension	5 (17.9)	0 (0.0)	15 (30.0)	7 (14.0)	0.306	0.047[a]
Rash	4 (14.3)	0 (0.0)	8 (16.0)	1 (2.0)	0.853	0.454
Hand-foot skin reaction	4 (14.3)	0 (0.0)	8 (16.0)	1 (2.0)	0.853	0.454
Abdominal pain	1 (3.6)	0 (0.0)	3 (6.0)	1 (2.0)	0.649	0.454
Bleeding	1 (3.6)	0 (0.0)	7 (14.0)	0 (0.0)	0.167	-
Fever	2 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0.059	-
Nausea	0 (0.0)	0 (0.0)	10 (20.0)	0 (0.0)	0.018[a]	-
Decreased appetite	1 (3.6)	0 (0.0)	12 (24.0)	0 (0.0)	0.033[a]	-
Diarrhea	0 (0.0)	0 (0.0)	10 (20.0)	0 (0.0)	0.018[a]	-
Fatigue	2 (7.1)	0 (0.0)	16 (32.0)	2 (4.0)	0.027[a]	0.290
Vomiting	0 (0.0)	0 (0.0)	8 (16.0)	0 (0.0)	0.034[a]	-
Proteinuria	8 (28.5)	0 (0.0)	5 (10.0)	0 (0.0)	0.053	-
Hyperbilirubinemia	6 (21.4)	0 (0.0)	11 (22.0)	0 (0.0)	0.958	-
Elevated ALT	2 (7.1)	0 (0.0)	8 (16.0)	0 (0.0)	0.293	-
Elevated AST	6 (21.4)	0 (0.0)	13 (26.0)	1 (2.0)	0.693	0.677
Hypoalbuminemia	2 (7.1)	0 (0.0)	7 (14.0)	0 (0.0)	0.391	-

[a]*P* value < 0.05, and it is statistically significant.
BeSiIT: Bevacizumab plus sintilimab plus interventional treatment; LeSiIT: Lenvatinib plus sintilimab plus interventional treatment; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

vomiting [8 (16.0%) *vs* 0, *P* = 0.034]. Grade 3-4 treatment-related cases of hypertension were more frequent in the LeSiIT group than in the BeSiIT group, and dose modifications were required to control blood pressure.

AFCE

The cutoff values of AFP and CEA were 28.0 and 3.60, respectively (the normal upper limits of AFP and CEA in Tianjin Medical University Cancer Institute and Hospital were 7.00 ng/mL and 5.00 ng/mL, respectively). The patients with low concentrations of AFP (≤ 28.0 ng/mL) and CEA (≤ 3.60 ng/mL) were assigned a score of 0. Patients with high concentrations of AFP (> 28.0 ng/mL) and CEA (> 3.60 ng/mL) were assigned a score of 1. After summing the AFP and CEA scores, all patients were subdivided into groups with AFCEs of 0, 1, or 2.

Cox regression analysis

The univariate and multivariate analysis results for PFS are listed in Table 4. Univariate analysis revealed that the independent factors associated with PFS were AFP concentrations (HR = 1.000; 95%CI: 1.000-1.000; *P* = 0.042) and AFCE (1 *vs* 0, HR = 3.255; 95%CI: 1.244-8.516; *P* = 0.016) (2 *vs* 0, HR = 6.153; 95%CI: 2.011-18.821; *P* = 0.001). Variables with *P* values < 0.05 were used for the multivariate analyses. Multivariate analysis revealed that AFCE was an independent factor associated with PFS (1 *vs* 0, HR = 2.973; 95%CI: 1.120-7.888; *P* = 0.029) (2 *vs* 0, HR = 5.746; 95%CI: 1.865-17.708; *P* = 0.002). Twenty-four patients had an AFCE of 0; 40 had an AFCE of 1; and 14 had an AFCE of 2. Patients with an AFCE of 0 had a PFS of less than the mPFS (95%CI: 14.0-NA), while the mPFS of patients with an AFCEs of 1 and 2 was 8 (95%CI: 6.0-NA) and 6 (95%CI: 3.0-NA) months, respectively. The mOS of patients with AFCEs at 0, 1, and 2 months was 17 (95%CI: 16.0-NA), 13 (95%CI: 12.0-NA), and 10 (95%CI: 3.0-NA), respectively. PFS (Figure 5A) and OS (Figure 5B) were statistically significant in patients with AFCE different AFCE patients (*P* values = 0.0019 and *P* = 0.012, respectively).

Stratified analyses were conducted based on the type of treatment administered. Figure 5C-F shows the PFS and OS curves for patients with varying AFCE in the BeSiIT and LeSiIT groups. Within the BeSiIT subgroup, seven patients had an AFCE of 0, 13 patients had an AFCE of 1, and eight patients had an AFCE of 2. Notably, there was a statistically significant disparity in the PFS curves among patients with different AFCE (*P* = 0.027; Figure 5C), and their OS curves were also statistically significant (*P* = 0.00069; Figure 5D). Within the LeSiIT subgroup, 17 patients exhibited an AFCE

Table 4 Univariate and multivariate Cox regression analysis of clinical characteristics with progression-free survival as the dependent variable

Independent variables	Univariate		Multivariate	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Group (LeSiIT/BeSiIT)	0.876 (0.460-1.670)	0.688		
Tumor size (> 10/≤ 10 cm)	1.143 (0.597-2.187)	0.687		
Tumor number (> 3/≤ 3)	0.759 (0.369-1.561)	0.453		
Gender (male/female)	0.969 (0.404-2.321)	0.943		
Age (years)	0.989 (0.961-1.017)	0.432		
Age (≥ 65/< 65 years)	0.878 (0.425-1.813)	0.725		
Etiology (yes/no)	0.559 (0.196-1.598)	0.278		
Liver cirrhosis (yes/no)	0.735 (0.375-1.440)	0.369		
Metastasis (yes/no)	0.767 (0.391-1.504)	0.440		
Vascular invasion (yes/no)	1.041 (0.554-1.957)	0.900		
Child-Pugh (B/A)	1.390 (0.655-2.951)	0.391		
BCLC stage (C/B)	0.869 (0.432-1.750)	0.694		
ECOG PS				
0	Reference	-		
1	1.562 (0.772-3.163)	0.215		
2	NA	0.972		
ALBI grade				
1	Reference	-		
2	0.668 (0.343-1.301)	0.235		
3	1.643 (0.382-7.069)	0.505		
AFP concentration (ng/mL)	1.000 (1.000-1.000)	0.042[a]	1.000 (1.000-1.000)	0.191
AFP (> 28.0/≤ 28.0 ng/mL)	1.754 (0.830-3.708)	0.141		
CEA (> 3.6/≤ 3.6 ng/mL)	1.645 (0.811-3.338)	0.168		
AFCE				
0	Reference	-	Reference	-
1	3.255 (1.244-8.516)	0.016[a]	2.973 (1.120-7.888)	0.029[a]
2	6.153 (2.011-18.821)	0.001[a]	5.746 (1.865-17.708)	0.002[a]

[a]*P* value less than < 0.05, and it is statistically significant.

PFS: Progression-free survival; HR: Hazard ratios; BeSiIT: Bevacizumab plus sintilimab plus interventional treatment; LeSiIT: Lenvatinib plus sintilimab plus interventional treatment; BCLC: The Barcelona Clinic Liver Cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status; NA: Not available; ALBI: Albumin-bilirubin; AFP: A-fetoprotein; CEA: Carcinoembryonic antigen; AFCE: A-fetoprotein and carcinoembryonic antigen score.

score of 0, 17 patients had an AFCE score of 1, and six patients had an AFCE score of 2. Notably, no statistically significant disparity was observed in the PFS (Figure 5E) and OS (Figure 5F) curves among patients with varying AFCE scores, as indicated by the respective *P*-values of 0.052 and 0.230. Within the BeSiIT subgroup, the 12-month areas under the curve of the AFCE was 0.809 (95%CI: 0.670-0.949; Figure 6).

DISCUSSION

HCC presents a formidable challenge to public health and is characterized by high incidence and mortality rates compared to other malignancies[1,2]. Unfortunately, most HCC cases are diagnosed at the intermediate to advanced stages, precluding the feasibility of surgical intervention[7,9]. However, the advent of targeted and immunotherapies has substantially broadened the therapeutic armamentarium for HCC, resulting in increasingly efficacious treatments[12,29,

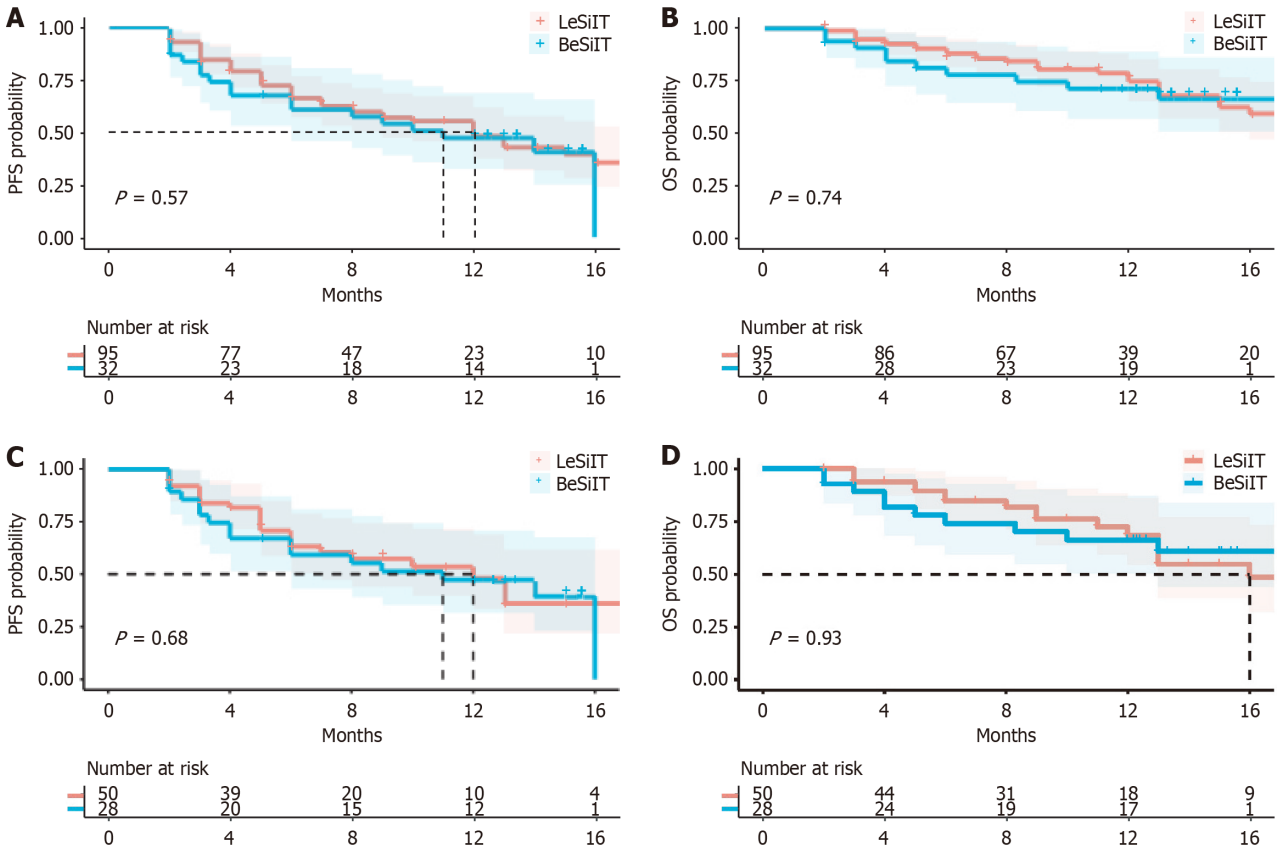

Figure 2 Kaplan-Meier curves between the lenvatinib plus sintilimab plus interventional treatment and bevacizumab plus sintilimab plus interventional treatment groups. A: Kaplan-Meier curves based on propensity score matching (PFS) before propensity score matching (PSM); B: Kaplan-Meier curves based on overall survival (OS) before PSM; C: Kaplan-Meier curves based on PFS after PSM; D: Kaplan-Meier curves based on OS after PSM. PFS: Progression-free survival; OS: Overall survival; PSM: Propensity score matching; BeSiIT: Bevacizumab plus sintilimab plus interventional treatment; LeSiIT: Lenvatinib plus sintilimab plus interventional treatment.

30]. Consequently, the therapeutic options for patients with intermediate and advanced HCC have progressively expanded.

In recent years, several studies have compared the efficacy of bevacizumab in combination with atezolizumab to that of lenvatinib in the treatment of unresectable HCC, and ultimately found no significant difference between the two in terms of prognosis[31,32]. Similarly, a retrospective study that combined TACE therapy with bevacizumab and atezolizumab versus lenvatinib alone found no difference in prognosis between the two groups[33]. However, all these studies were conducted on bevacizumab combination immunotherapy versus lenvatinib monotherapy. Therefore, whether a combination of lenvatinib and immunotherapy can achieve better efficacy remains controversial. To control confounding variables, patients who received both sintilimab and interventional therapy were selected to compare the differences in efficacy between lenvatinib and bevacizumab.

The LeSiIT and BeSiIT groups had comparable PFS (12.0 *vs* 11.0 months), OS (16 months *vs* not reached), and ORR (60.7% *vs* 46.0% according to the RECIST criteria; 60.7% *vs* 58.0% according to the mRECIST criteria) in this study. Survival curves revealed no significant differences in OS and PFS between the two groups, either before or after PSM. Both LeSiIT and BeSiIT groups had manageable toxicity profiles. The patients treated with LeSiIT had a higher risk of TRAEs of any grade than those treated with BeSiIT alone. Additionally, the BeSiIT group had a higher conversion rate than the LeSiIT group (57.1% *vs* 26.0%).

The LeSiIT group seemed to have a high risks of any grade of TRAEs, such as nausea, decreased appetite, diarrhea, fatigue, and vomiting, although lenvatinib dose was 8 mg to reduce the risk of adverse events (standard dose: 8-12 mg according to body weight). Consistent with previous reports, thrombocytopenia, proteinuria, hyperbilirubinemia, and elevated aspartate aminotransferase (AST) were the most common TRAEs associated with BeSiIT, whereas fatigue, hypertension, elevated AST, and decreased appetite were the most common TRAEs associated with LeSiIT[12,17,22,23]. As lenvatinib acts as a multi-target TKI, there is a greater proportion of treatment-related adverse effects than bevacizumab, which is also consistent with the literature[31]. However, these TRAEs were not unexpected and were managed by dose modification or treatment interruption.

Systemic antitumor therapy combined with local therapy is expected to improve the tumor remission and conversion rates. An ORR of approximately 58.0%, DCR of 68.0%, mPFS of 12.0 months, and a conversion rate of 26.0% were observed in the LeSiIT group. Lenvatinib inhibits tumor angiogenesis by comprehensively blocking the VEGFR 1-3 signaling pathway, leading to tumor "starvation" and hypoxia, which also results in growth inhibition or death and

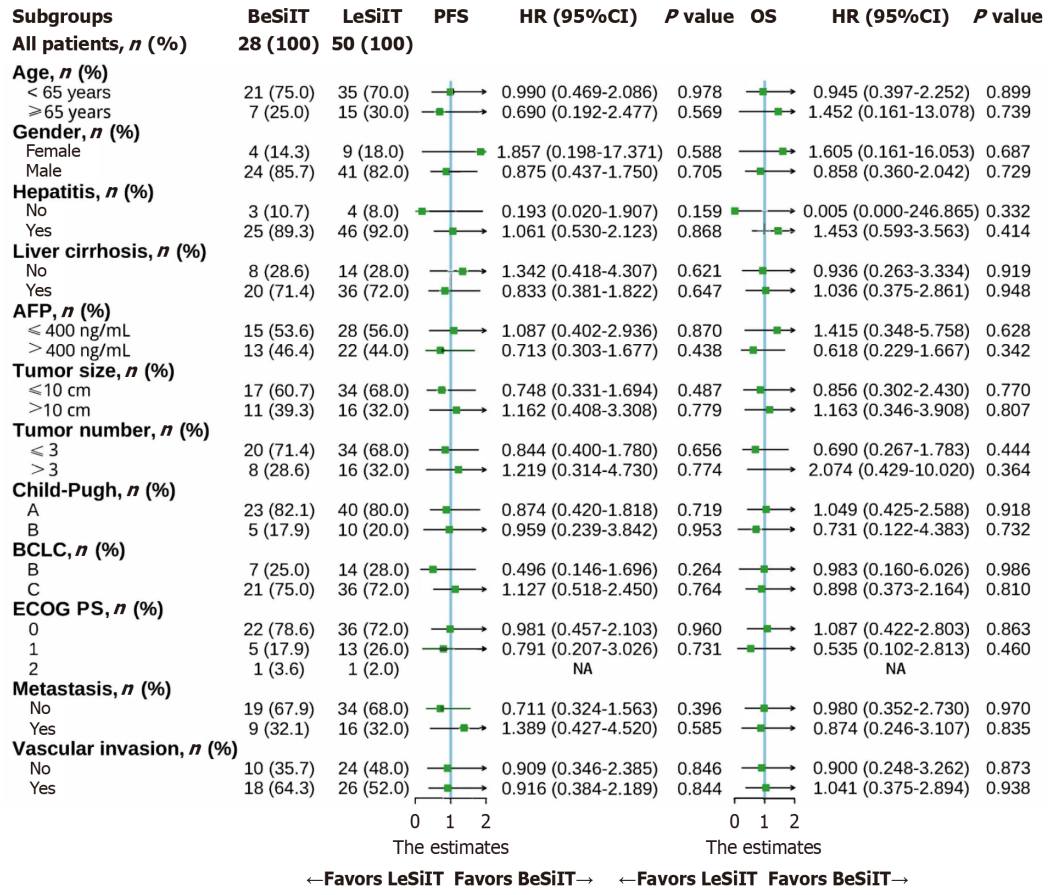

Figure 3 Forest plot for progression-free survival and overall survival of the matched cohorts of patients. BeSiIT: Bevacizumab plus sintilimab plus interventional treatment; LeSiIT: Lenvatinib plus sintilimab plus interventional treatment; PFS: Progression-free survival; OS: Overall survival; HR: Hazard ratios; AFP: A-fetoprotein; BCLC: The Barcelona Clinic Liver Cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status.

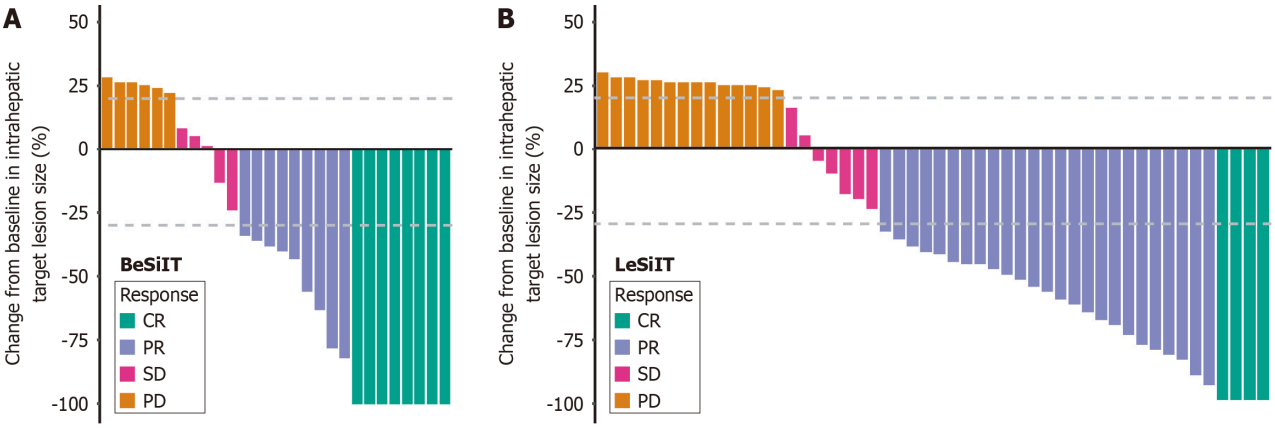

Figure 4 Best percentage changes in the sizes of the intrahepatic target lesions of patients from baseline assessed with modified response evaluation criteria in solid tumors. A: Bevacizumab plus sintilimab plus interventional treatment; B: Lenvatinib plus sintilimab plus interventional treatment. The horizontal coordinate represents each patient and the vertical coordinate represents the percentage change in intrahepatic target lesion size from baseline. BeSiIT: Bevacizumab plus sintilimab plus interventional treatment; LeSiIT: Lenvatinib plus sintilimab plus interventional treatment; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease.

regulates the tumor immune microenvironment by inhibiting the VEGF pathway[34,35]. It also plays an immunomodulatory role by blocking FGFR4, reducing tumor PD-1 expression, and inhibiting Treg differentiation[36,37]. The combination of lenvatinib and interventional treatment has been reported to have remarkable effects on prolonging the OS of patients[38]. An explanation for the survival benefits of the LeSiIT group is that lenvatinib combined with interventional treatment forms a beneficial tumor-immune microenvironment by blocking immunosuppressive VEGF signaling [39], which can enhance the clinical efficacy of PD-1 antibodies by reducing the blood supply to HCC and activating the release of tumor-specific antigens[40,41].

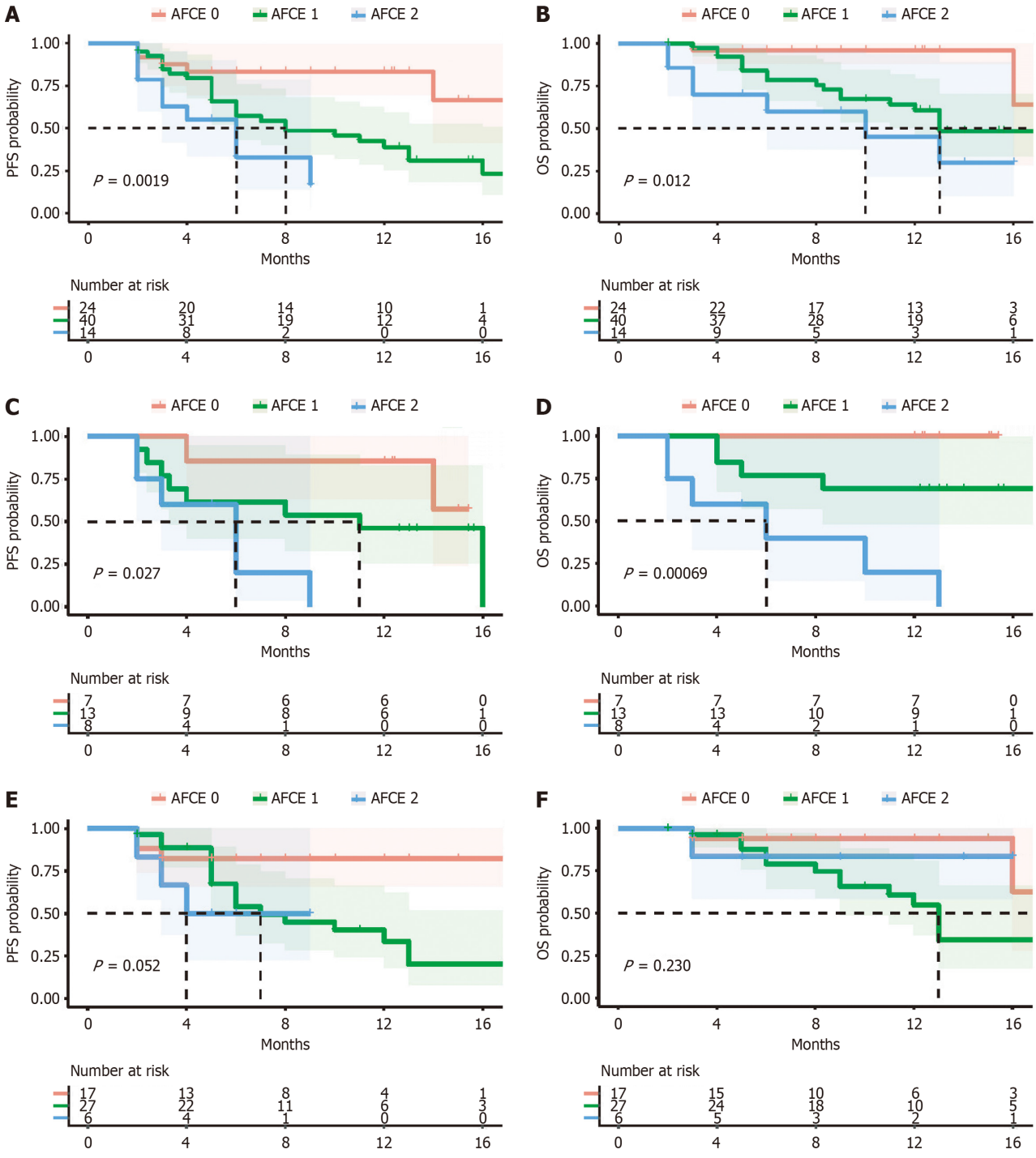

Figure 5 Kaplan-Meier curves based on α-fetoprotein and carcinoembryonic antigen score. A: Kaplan-Meier curves based on progression-free survival (PFS); B: Kaplan-Meier curves based on overall survival (OS); C: Kaplan-Meier curves based on PFS in the bevacizumab plus sintilimab plus interventional treatment (BeSiIT) groups; D: Kaplan-Meier curves based on OS in the BeSiIT groups; E: Kaplan-Meier curves based on PFS in the lenvatinib plus sintilimab plus interventional treatment (LeSiIT) groups; F: Kaplan-Meier curves based on OS in the LeSiIT groups. AFCE: A-fetoprotein and carcinoembryonic antigen score; PFS: Progression-free survival; OS: Overall survival.

The ORR, DCR, mPFS, and conversion rates in the BeSiIT group were 60.7%, 78.6%, 11.0 months, and 57.1%, respectively, which were better than those of most reported triple therapies. The improved treatment effects observed in the BeSiIT group may be due to the synergistic antitumor effect of bevacizumab, sintilimab, and the interventional treatment. Anti-VEGF drugs can reduce CD4+ regulatory T lymphocytes and myeloid-derived suppressor cells, and inhibit the activation and differentiation of dendritic cells. The combination of a PD-1 inhibitor and an anti-VEGF drug may change the cold tumor into a hot tumor, which increases the tumor-cytotoxicity effect[42]. Interventional chemotherapeutic agents can increase human leukocyte antigen expression and augment T-cell stimulation, consequently activating the adaptive immune system[43]. It can also disrupt signal transducers and activate transcription 6-mediated immunosuppression to recover immunosurveillance[44].

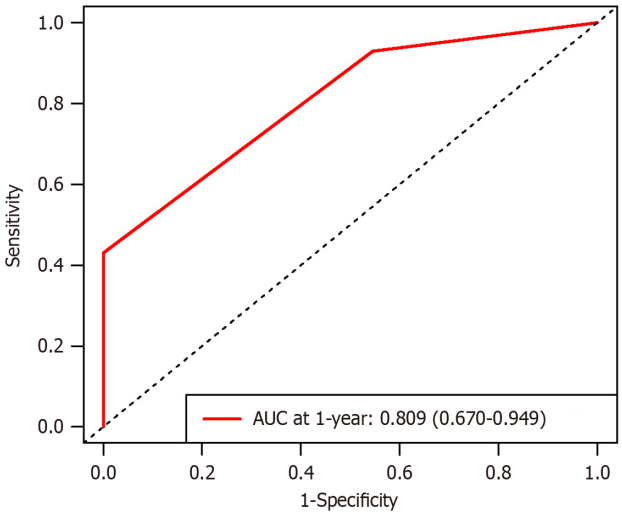

Figure 6 Receiver operating characteristic curves for α-fetoprotein and carcinoembryonic antigen score in the bevacizumab plus sintilimab plus interventional treatment subgroup. AUC: Area under the curve.

In recent studies, no significant difference in prognosis has been found between lenvatinib monotherapy and bevacizumab combination immunotherapy. In our study, even with combination immunotherapy, lenvatinib failed to show a better prognosis compared that with bevacizumab combination immunotherapy, while leading to a higher rate of adverse reactions.

Conversion therapy refers to the transformation of an unresectable HCC into resectable disease, followed by surgical removal of the tumor[9]. Unresectable HCC can be divided into two categories. One category is unresectable in terms of surgery, and the patient's systemic condition cannot withstand surgical trauma, liver function intolerance, or insufficient volume of the remaining liver (surgically unresectable). Another unresectable liver cancer will be technically resectable; however, the effect of resection is no better than that of nonsurgical treatment (oncologically/biologically unresectable). While the definition of surgically unresectable HCC is widely accepted, the definition of oncologic/biologically unresectable HCC is dynamic and controversial. However, the long-term benefits of OS are much more important than successful excision[7]. In this study, although the conversion rate in the BeSiIT group was higher than that in the LeSiIT group (57.1% *vs* 26.0%), the PFS and OS of the two groups were not statistically significant. The different conversion rates of the groups may be attributed to the different formulations used in the two treatments.

Although there was no significant difference in the long-term prognosis between the two groups, the BeSiIT group was superior to the LeSiIT group in terms of both adverse effects and conversion rates. Compared to bevacizumab, lenvatinib, a multi-targeted TKI, has relatively few effective second-line therapies following resistance to its first-line treatment. Therefore, bevacizumab immunotherapy combined with interventional therapy may be a better treatment option for patients with advanced, unresectable HCC. However, because bevacizumab can exacerbate bleeding tendencies, a similar prognosis can be achieved by administering lenvatinib plus immunotherapy, in combination with interventional therapy, for severe esophagogastric fundal varices secondary to cirrhosis.

Multivariate analysis revealed that AFCE was an independent factor associated with PFS. AFP is a clinical biomarker widely used to diagnose HCC, and high concentrations of AFP are closely associated with poor prognosis and a high risk of HCC development[45]. Inhibition of apoptosis plays an essential role in the development of malignancy, and AFP can inhibit cell apoptosis through the p53/Bax/caspase-3 apoptotic signaling pathway[46]. In addition, AFP can interact with a cancer suppressor gene, phosphate, and a tension homolog deleted on chromosome 10, activating the PI3K/AKT/mTOR pathway and inhibiting HCC cell autophagy to promote malignant behavior by upregulating the expression of the autophagy-related protein mTOR[47]. CEA, a relatively non-specific antigen, is widely used in the clinical diagnosis and management of gastrointestinal cancers[48]. High levels were found to be an independent predictor of poor prognosis in patients with HCC[49]. Previous research established the aggregate of AFP, CA19-9, and CEA scores as the tumor marker score (TMS) and identified a connection between TMS and tumor prognosis[50]. In this study, AFCE was based on the AFP and CEA levels. Notably, in the univariate analysis, neither AFP nor CEA scores demonstrated significance, whereas the combined score of the two was acknowledged as an autonomous risk factor linked to progression in the multivariate analysis. The risk of 1-year progression was 2.855 times higher in the AFCE 1 than that in the AFCE 0 groups (HR: 2.973; 95%CI: 1.120-7.888; P = 0.029) and 4.686 times higher in the AFCE 2 than for the AFCE 0 group (HR: 5.746; 95%CI: 1.865-17.708; P = 0.002). Plotting of the survival curves revealed a significant difference in the survival curves of patients in the BeSiIT group with different AFCE scores; however, there was no significant difference in the LeSiIT group. In the BeSiIT group, the area under the curve for AFCE was 0.809, indicating that the use of AFCE adequately predicted 1-year progression in patients with intermediate-advanced stage HCC treated with BeSiIT. Based on the findings of this study, AFCE was significantly correlated with the prognostic outcomes of patients diagnosed with intermediate and advanced HCC who underwent BeSiIT treatment. Furthermore, a lower pretreatment AFCE value was indicative of a more favorable prognosis for these patients. AFCE, a metric derived from commonly used tumor markers, offers a straightforward computational process and holds potential as a novel prognostic predictor for patients with intermediate and

advanced HCC who receive molecularly targeted immunotherapies and interventional therapies.

The present study had several limitations. First, this was a retrospective single-center study, and selection bias was inevitable, although the baseline characteristics of the two cohorts were well-balanced after PSM. Secondly, the sample size was relatively small. A prospective randomized controlled trial involving several centers is required to validate the findings of this study. Third, subsequent treatments may have been confounding factors; however, the details were not reported in this study. Finally, long-term survival data were lacking because half of the patients did not progress to the last data cut-off point.

CONCLUSION

BeSiIT and LeSiIT showed acceptable toxicities, and patients treated with them demonstrated comparable PFS, OS, and ORR. However, the BeSiIT group had a better conversion rate than the LeSiIT group. AFCE is associated with the prognosis of patients with intermediate-to-advanced unresectable HCC treated with BeSiIT.

FOOTNOTES

Author contributions: Song TQ, Chen L, Han RY, Gan LJ and Lang MR conceptualized and designed the research; Gan LJ, Han RY and Lang MR screened patients and acquired clinical data; Gan LJ, Chen L, Han RY, Lang MR, Ren SH, Li GT, Liu YY, Tian XD, Zhu KW, Sun LY, and Liu DM performed Data analysis; Song TQ, Chen L and Han RY wrote the paper. All the authors have read and approved the final manuscript. Han RY designed, acquired clinical data, performed data analysis and prepared the first draft of the manuscript. Gan LJ was responsible for patient screening, enrollment, collection and analysis of clinical data. Both authors have made crucial and indispensable contributions towards the completion of the project and thus qualified as the co-first authors of the paper. Both Song TQ and Chen L have played important and indispensable roles in the experimental design and manuscript preparation as the co-corresponding authors. Song TQ applied for and obtained the funds for this research project. Song TQ conceptualized, designed, and supervised the whole process of the project. Chen L was instrumental and responsible for data re-analysis and re-interpretation and figure plotting. This collaboration between Song TQ and Chen L is crucial for the publication of this manuscript and other manuscripts still in preparation.

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