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ORIGINAL RESEARCH

Low-Dose Versus Standard-Dose Bevacizumab Plus Sintilimab for Unresectable Hepatocellular Carcinoma: A Real-World Comparative Study of Efficacy and Safety

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Background/Aim: Sintilimab combined with bevacizumab (Sinti-Bev) is recommended as first-line treatment for unresectable hepatocellular carcinoma (uHCC) in China. However, the IMbrave150 and ORIENT-32 trials reported treatment-related adverse events (TRAEs) leading to bevacizumab interruption or discontinuation. Therefore, we aimed to explore the clinical impact of low-dose bevacizumab combined with sintilimab as a first-line therapy in patients with uHCC.

Patients and Methods: A total of 85 patients who received Sinti-Bev as first-line therapy were retrospectively analyzed. Patients were stratified into low-dose (7.5 mg/kg, n=47) and high-dose (15 mg/kg, n=38) groups according to bevacizumab dosage. Antitumor efficacy, TRAEs incidence, and treatment duration were compared between groups. Inverse probability of treatment weighting (IPTW) was applied to balance baseline covariates.

Results: In our study, although 91.8% of patients received Sinti-Bev combined with transarterial therapy (TAT), there was no significant difference in the number of TAT between groups. The low-dose group did not show significantly shorter progression-free survival (PFS: 9.4 vs.10.5 months, P = 0.837) and objective response rate (ORR: 61.70% vs. 63.16%, P = 0.890) compared with the high-dose group. Nevertheless, the overall survival (OS) rates in the low-dose group were numerically higher than those in the high-dose group (6/12/18 months: 94%/77%/55% vs. 91%/71%/48%). Post-IPTW analyses yielded consistent findings. Importantly, the incidence of esophagogastric variceal (EGV) bleeding was numerically lower in the low-dose group (10.6% vs. 21.1%), with fewer grade ≥3 bleeding events (6.38% vs. 18.42%). After IPTW adjustment, the median treatment duration was approximately 2.5 months longer in the low-dose group (12.0 vs. 9.5 months).

Conclusion: Compared to high-dose bevacizumab combined with sintilimab, the low-dose regimen showed no significant differences in PFS, OS, or ORR, while improving safety and treatment continuity. Low-dose bevacizumab may serve as a safer alternative dose for uHCC patients with increased bleeding risk.

Keywords: bevacizumab, bleeding, hepatocellular carcinoma, low-dose, sintilimab

Introduction

Liver cancer ranks as the third leading cause of cancer-related mortality worldwide, following lung cancer and colorectal cancers, and is the sixth most common malignancy.[1] Hepatocellular carcinoma (HCC) accounts for approximately 75–85% of primary liver cancers, with China contributing more than half of the global disease burden.[2] Early-stage HCC is primarily managed with potentially curative treatment, such as surgical resection or local ablation.[3]

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Unfortunately, most patients are diagnosed at an advanced disease, rendering curative surgery infeasible. Approximately 50–60% of patients with HCC require systemic therapy during the course of their disease, with roughly half presenting with advanced-stage disease at diagnosis and the remainder progressing after failure of early-stage treatments.[4,5]

Bevacizumab, a recombinant humanized monoclonal antibody targeting vascular endothelial growth factor A (VEGF-A), inhibits tumor angiogenesis and proliferation by blocking the interaction between VEGF-A and VEGF receptor-2 on endothelial cells.[6] It has been widely applied in the treatment of colorectal cancer, non-small cell lung cancer, ovarian cancer, and other malignancies.[7] In HCC, the combination of atezolizumab with bevacizumab (Atezo-Bev) has ushered in a new era of synergistic targeted immunotherapy. The IMbrave150 trial demonstrated that Atezo-Bev significantly improved survival outcomes compared with sorafenib monotherapy,[8] with the Chinese subgroup achieving a median OS (mOS) of up to 24 months—substantially exceeding the global outcomes.[9] Similarly, the ORIENT-32 trial confirmed that Sinti-Bev as first-line treatment provided substantial clinical benefit over sorafenib, achieving a higher ORR (24% vs. 8%).[10] Moreover, real-world studies have further validated the efficacy and safety of bevacizumab combined with immune checkpoint inhibitors (ICIs), particularly when integrated with TAT such as transarterial chemoembolization (TACE) or hepatic arterial infusion chemotherapy (HAIC), yielding promising survival benefits with ORRs exceeding 60%.[11–13]

However, excessive VEGF inhibition may induce vascular regression, endothelial fragility, and hypoxia, potentially increasing the risk of bleeding and limiting therapeutic synergy.[14] In HCC, the clinical application of bevacizumab presents distinct challenges. Unlike many other solid tumors, most patients with HCC—particularly in China—have underlying liver cirrhosis (LC). Epidemiological data indicate that over 80% of patients with HCC in China, the majority of whom are infected with hepatitis B or C virus (HBV/HCV), also have LC, and approximately 90% of those with LC develop portal hypertension (PH).[2] Prolonged bevacizumab exposure in this population may further exacerbate PH.[15] Moreover, EGV and elevated PH markedly increase susceptibility to hemorrhagic complications. In this setting, high-dose anti-VEGF therapy may exacerbate vascular endothelial dysfunction, thereby increasing the risk of AEs.

Furthermore, previous studies have indicated that the incidence of TRAEs is partially dose dependent.[16,17] Notably, the recommended bevacizumab dose for HCC (15 mg/kg)[8,10] exceeds that used for other solid tumors (5–10 mg/kg),[18–20] raising safety concerns in patients with HCC and underlying liver cirrhosis and portal hypertension.[21,22] For instance, in Phase II HCC trials lacking standardized prophylactic management of EGV, approximately 10% of bevacizumab-treated patients experienced PH-related bleeding events.[23] When bevacizumab-related AEs occur, temporary treatment interruption or switching to alternative regimens may be necessary. However, frequent interruptions may reduce antitumor efficacy and accelerate disease progression.[24,25] Fortunately, evidence from other malignancies suggests that reduced-dose bevacizumab may preserve antitumor efficacy while mitigating toxicity. Gleeson et al reported that the OS did not significantly differ between patients receiving reduced-dose bevacizumab (one-third or one-half of the standard dose) and those receiving the standard dose in progressive glioblastoma.[26] Similarly, Suminokura et al found that low-dose bevacizumab not only improved prognosis but also reduced the incidence of bevacizumab-related AEs in ovarian cancer.[27] Therefore, we hypothesize that low-dose bevacizumab combined with sintilimab may maintain survival outcomes in patients with uHCC by minimizing treatment interruptions and prolonging cumulative treatment exposure.

To test this hypothesis, we conducted a real-world retrospective study evaluating the efficacy and safety of low-dose bevacizumab combined with sintilimab as first-line therapy for patients with uHCC. Clinical outcomes and safety profiles were compared between patients receiving low-dose bevacizumab (7.5 mg/kg) plus sintilimab and those receiving the standard-dose regimen (15 mg/kg), with baseline confounders balanced using IPTW.

Materials and Methods

Study Design and Population

This retrospective multicenter study was conducted between May 2022 and June 2024 at three tertiary medical institutions in China: the Second Affiliated Hospital of Nanchang University, the First Affiliated Hospital of Gannan Medical University, and the Fifth People's Hospital of Ganzhou. Patients with uHCC who received Sinti-Bev were

enrolled. Clinical data were collected from inpatient and outpatient medical records and supplemented by telephone follow-up.

Inclusion criteria: (a) Diagnosis of uHCC confirmed by imaging (enhanced computed tomography [CT] or magnetic resonance imaging [MRI]) or pathological examination; (b) Treatment with Sinti-Bev; (c) Child-Pugh class A or B; (d) Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1; (e) At least one measurable lesion on CT or MRI evaluated according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Exclusion criteria: (a) Prior systemic therapy for HCC; (b) Severe comorbid conditions compromising treatment tolerance; (c) Concomitant malignancies; (d) Incomplete follow-up data; (e) Insufficient treatment cycles for efficacy evaluation; (f) Treatment interruption exceeding two cycles for non-medical reasons.

Treatment Procedure

Transarterial Therapy (TAT)

In our study, most patients (91.8%) underwent TAT (TACE and/or HAIC) which were jointly administered by two senior physicians. All patients received guideline-recommended TAT based on tumor burden, tumor size and location, tumor vascular supply, macrovascular invasion, liver function status, and ECOG PS score.

TACE

Under digital subtraction angiography (DSA) guidance, the catheter was superselectively advanced into tumor-feeding artery. According to the Chinese expert consensus, intra-arterial chemotherapeutic drug administration for TACE was performed with lobaplatin (30 mg/m^2) and 5-fluorouracil (1000 mg), followed by embolization using a lipiodol emulsion (10–20 mL) mixed with doxorubicin (50 mg).[28] The specific doses of chemotherapeutic agents and iodized oil were individualized based on a comprehensive assessment of body surface area, tumor size and location, tumor vascularity, liver function status, and intra-procedural angiographic findings.

HAIC

Considering the limited efficacy of TACE in patients with multinodular, massive, or diffuse HCC involving multiple feeding arteries, eligibility for HAIC or TACE combined with HAIC (TACE-HAIC) was jointly determined by two senior physicians. The catheter was superselectively inserted into tumor-supplying arteries under DSA guidance for HAIC with the FOLFOX regimen. This regimen consisted of oxaliplatin (85 mg/m^2) infused over 3 hours on day 1, leucovorin (400 mg/m^2) administered over 3–5 hours on day 1, a bolus of 5-fluorouracil (400 mg/m^2), and followed by continuous infusion of 5-fluorouracil (2400 mg/m^2) over 46 hours.

TACE-HAIC

For TACE-HAIC, chemoembolization was first performed in selected tumor-feeding arteries based on tumor vascularity and liver function using the above method. Subsequently, the catheter was super-selectively positioned in the tumor-supplying arteries, and patients returned to the ward for HAIC administration with the FOLFOX regimen as described above.

Usually, TAT was repeated every 3–4 weeks. The need for repeat TAT was determined according to liver function status, ECOG PS score, alpha-fetoprotein (AFP) levels and contrast-enhanced CT or MRI finding to evaluate tumor viability. After comprehensive assessment, the interval of TAT could be extended and the dosage of chemotherapeutic agents can be adjusted to ensure the safe of treatment.

Sinti-Bev Treatment Protocol

Patients received sintilimab (200 mg intravenously every 3 weeks) in combination with bevacizumab at either 7.5 mg/kg (low-dose group) or 15 mg/kg (high-dose group), administered every 3 weeks. For patients receiving TAT, Sinti-Bev was initiated within 3–5 days after the procedure. The selection of bevacizumab dose was determined by treating physicians based on baseline liver function, presence of PH, variceal status, platelet count, bleeding risk, overall clinical condition, and economic conditions, reflecting real-world clinical practice in cirrhosis-dominant HCC populations. The doses of

sintilimab and bevacizumab could be appropriately reduced, temporarily interrupted, or permanently discontinued based on TRAEs. Treatment continued until disease progression, unacceptable toxicity, or death.

Data Collection

Baseline and follow-up data were extracted from electronic medical records for analysis. The variables encompassed age, gender, ECOG PS score, etiology, AFP, platelet count, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, Child-Pugh classification, Albumin-Bilirubin (ALBI) grade, concurrent LC, tumor count, maximum tumor diameter, hepatic vein tumor thrombus (HVTT), portal vein tumor thrombus (PVTT), extrahepatic metastasis, TAT type, bevacizumab dose, and TRAEs. Laboratory tests and contrast-enhanced CT or MRI imaging was performed within 7 days before treatment initiation. Imaging was repeated every 2–3 months and independently reviewed by two radiologists.

Outcome Assessment

Tumor response was assessed using Contrast-enhance CT or MRI imaging every 2–3 months after combination therapy. The primary endpoints were PFS and ORR, while secondary endpoints included OS and AEs. PFS was defined as the time from treatment initiation to disease progression or death from any cause, and OS as the time from treatment initiation to death from any cause. Treatment duration was defined as the period from first dose of Sinti-Bev to treatment discontinuation due to progression, death, or toxicity. Tumor responses were classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to RECIST 1.1 and modified RECIST (mRECIST) criteria. ORR reflected the proportion of patients achieving CR or PR, and Disease control rate (DCR) as the proportion of patients achieving CR, PR, or SD. TRAEs were graded using Common Terminology Criteria for Adverse Events version 5.0 criteria.

Statistical Analysis

Statistical analysis was performed using R (version 4.4.1) and IBM SPSS Statistics (version 27.0). The normality of continuous variables was assessed with Shapiro–Wilk test. Non-normally distributed variables were reported as medians (interquartile range), and categorical variables as frequency (n, %). Intergroup comparisons were conducted using independent–samples t-tests for continuous data and Pearson χ^2-test or Fisher's exact test for categorical data. PFS and OS were estimated using the Kaplan–Meier method and compared with the Log rank test. Variables with $P < 0.05$ in univariate analysis were included in Cox proportional hazards models for multivariate analysis to calculate hazard ratios (HR) with 95% confidence intervals (CI). All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

To minimize the impact of potential confounding factors, IPTW was employed. Propensity scores (PS) were estimated for all baseline characteristics by multivariable logistic regression model, with weights defined as 1/PS for the high-dose group and 1/(1-PS) for the low-dose group. Differences in PFS and OS between the low-dose and high-dose groups were compared using weighted Kaplan–Meier estimates with IPTW. We used the weighted Log rank test to examine significance of difference between groups. A weighted Cox proportional hazards model with IPTW was used to identify prognostic factors associated with PFS and OS.

Results

Baseline Characteristics of Patients

Between May 2022 and June 2024, 85 eligible patients were retrospectively included in the final analysis from a cohort of 161 patients with uHCC who received Sinti-Bev, including 47 patients in the low-dose group and 38 patients in the high-dose group (Figure 1).

Baseline characteristics were generally comparable between groups (Table 1), except for a significant difference in the type of TAT (P = 0.002). Overall, 78 patients (91.8%) received combined TAT, with TACE or TACE-HAIC predominantly administered in the high-dose group, whereas TACE-based combinations were more frequently used

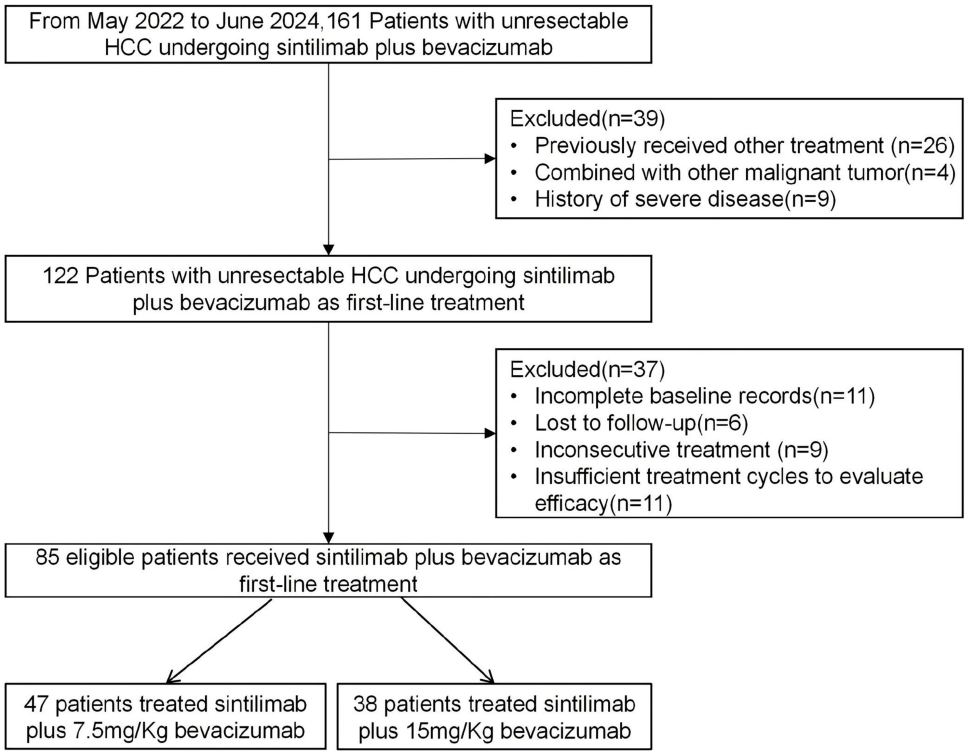

Figure 1 Patient flow chart.

in the low-dose group. The high-dose group contained a higher proportion of patients with LC, Child–Pugh class B, extrahepatic spread, and BCLC stage C compared with the low-dose group. Although numerically higher proportions of advanced clinical features were observed in the high-dose group, baseline differences were not statistically significant, and were further balanced after IPTW adjustment. The median number of Sinti-Bev treatment cycles was 8 in the low-dose group and 7 in the high-dose group (P = 0.150), while the median number of TAT procedures was 2 and 3, respectively (P = 0.179).

Table 1 Baseline Characteristics of Patients Before and After IPTW

Variables	Before IPTW			After IPTW		
	Low-Dose (n=47)	High-Dose (n=38)	*P*	Low-Dose (n=78.21)	High-Dose (n=77.14)	*P*
Age(years)			0.822			0.853
<60	27 (57.45)	20 (52.63)		44.64 (57.08)	42.30 (54.84)	
≥60	20 (42.55)	18 (47.37)		33.56 (42.92)	34.84 (45.16)	
Gender			0.617			0.782
Male	42 (89.36)	36 (94.74)		71.35 (91.23)	71.74 (93.00)	
Female	5 (10.64)	2 (5.26)		6.86 (8.77)	5.40 (7.00)	
ECOG/PS			0.831			0.941
0	30 (63.83)	26 (68.42)		50.81 (64.96)	49.44 (64.10)	
1	17 (36.17)	12 (31.58)		27.40 (35.04)	27.70 (35.90)	
Etiologies of liver disease			1.000			0.935
Other	4 (8.51)	3 (7.89)		6.48 (8.29)	6.00 (7.78)	
HBV	43 (91.49)	35 (92.11)		71.72 (91.71)	71.14 (92.22)	

(*Continued*)

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Table 1 (Continued).

Variables	Before IPTW			After IPTW		
	Low-Dose (n=47)	High-Dose (n=38)	*P*	Low-Dose (n=78.21)	High-Dose (n=77.14)	*P*
Liver cirrhosis			0.490			0.494
Absent	10 (21.28)	5 (13.16)		13.30 (17.01)	9.07 (11.76)	
Present	37 (78.72)	33 (86.84)		64.91 (82.99)	68.07 (88.24)	
Child–Pugh classification			0.295			0.599
A	44 (93.62)	32 (84.21)		72.30 (92.44)	68.67 (89.03)	
B	3 (6.38)	6 (15.79)		5.91 (7.56)	8.46 (10.97)	
ALBI classification			0.877			0.980
1	13 (27.66)	12 (31.58)		23.69 (30.29)	23.59 (30.58)	
2	34 (72.34)	26 (68.42)		54.52 (69.71)	53.55 (69.42)	
AST (U/L)			0.506			0.848
<40	14 (29.79)	8 (21.05)		22.20 (28.39)	20.24 (26.24)	
≥40	33 (70.21)	30 (78.95)		56.00 (71.61)	56.90 (73.76)	
ALT (U/L)			0.968			
<50	31 (65.96)	24 (63.16)		52.39 (66.98)	49.24 (63.84)	0.789
≥50	16 (34.04)	14 (36.84)		25.82 (33.02)	27.90 (36.16)	
Alpha-fetoprotein (ng/mL)			0.904			0.692
<400	24 (51.06)	18 (47.37)		38.71 (49.49)	34.46 (44.67)	
≥400	23 (48.94)	20 (52.63)		39.50 (50.51)	42.68 (55.33)	
Maximum tumor size(cm)			0.787			0.744
<10	21 (44.68)	19 (50.00)		36.77 (47.01)	39.35 (51.02)	
≥10	26 (55.32)	19 (50.00)		41.44 (52.99)	37.79 (48.98)	
Intrahepatic tumor number			0.678			0.723
<3	13 (27.66)	13 (34.21)		24.58 (31.43)	27.48 (35.62)	
≥3	34 (72.34)	25 (65.79)		53.62 (68.57)	49.66 (64.38)	
HVTT			1.000			0.991
Absent	36 (76.60)	29 (76.32)		61.42 (78.53)	60.67 (78.65)	
Present	11 (23.40)	9 (23.68)		16.79 (21.47)	16.47 (21.35)	
PVTT			1.000			0.916
Absent	24 (51.06)	20 (52.63)		41.32 (52.83)	41.74 (54.11)	
Present	23 (48.94)	18 (47.37)		36.89 (47.17)	35.40 (45.89)	
Extrahepatic spread			0.219			0.706
Absent	32 (68.09)	20 (52.63)		49.68 (63.53)	45.54 (59.03)	
Present	15 (31.91)	18 (47.37)		28.53 (36.47)	31.60 (40.97)	
BCLC			0.673			0.990
A	4 (8.51)	4 (10.53)		10.26 (13.12)	10.93 (14.17)	
B	11 (23.40)	6 (15.79)		17.28 (22.10)	16.25 (21.07)	
C	32 (68.09)	28 (73.68)		50.66 (64.78)	49.96 (64.76)	
Local therapy			0.002			0.378
Absent	4 (8.51)	3 (7.89)		7.89 (10.09)	6.51 (8.44)	
HAIC	0 (0.00)	5 (13.16)		0.00 (0.00)	5.00 (6.48)	
TACE	35 (74.47)	15 (39.47)		52.13 (66.66)	43.99 (57.03)	
TACE-HAIC	8 (17.02)	15 (39.47)		18.18 (23.25)	21.64 (28.05)	
Sinti-Bev cycles	8.00 [6.00, 12.50]	7.00 [4.00, 14.00]	0.150	9.00 [6.00, 11.80]	7.00 [4.00, 14.00]	0.162
TAT number	2.00 [2.00, 3.00]	3.00 [2.00, 4.00]	0.179	2.00 [2.00, 3.22]	2.00 [2.00, 4.00]	0.752

Notes: Data are shown as absolute value and percentage or median and interquartile range. Post-IPTW sample sizes (n=78.21, n=77.14) are weighted values.
Abbreviations: low-dose, Sintilimab plus 7.5 mg/Kg Bevacizumab; high-dose, Sintilimab plus 15 mg/Kg Bevacizumab; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBV, Hepatitis B Virus; ALBI, Albumin-Bilirubin; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; HVTT, Hepatic Vein Tumor Thrombus; PVTT, Portal Vein Tumor Thrombus; BCLC, Barcelona Clinic Liver Cancer Staging System; HAIC, Hepatic Arterial Infusion Chemotherapy; TACE, Transarterial Chemoembolization; TACE-HAIC, TACE combined with HAIC; Sinti-Bev, Sintilimab plus Bevacizumab; TAT, Transarterial Therapy.

After IPTW adjustment, no significant differences were observed in potential confounding variables, indicating successful covariate balance between the two groups. Five patients in the high-dose group received combined HAIC, whereas none in the low-dose group did. The median number of Sinti-Bev treatment cycles increased to 9 in the low-dose group and remained 7 in the high-dose group (P = 0.162); whereas the median number of TAT procedures was 2 in both groups (P = 0.752). Although these differences did not reach statistical significance, the numerically higher number of Sinti-Bev treatment cycles in the low-dose group may indicate improved tolerability and treatment adherence. In contrast, the comparable number of TAT procedures between groups suggests balanced locoregional treatment intensity, minimizing the likelihood that differences in transarterial interventions confounded survival comparisons.

Survival Analysis and Treatment Response for All Patients

As of the last follow-up on June 15, 2024, the median follow-up duration was 14.8 months (95% CI:12.9–17.5, reverse Kaplan-Meier method). Overall, 54 patients experienced disease progression and 29 patients died. The median PFS (mPFS) was 10.0 months (95% CI:7.8–13.7) and the mOS was 23.4 months (95% CI:14.1–NA) (Figure 2A and B). According to the mRECIST criteria, 9 patients (10.59%) achieved CR, 44 patients (51.76%) had PR, 27 patients (31.76%) showed SD, and 5 patients (5.88%) developed PD, resulting in ORR of 62.35% and DCR of 94.12% (Table 2). Based on the RECIST 1.1 criteria, 41 patients (48.24%) achieved ORR and 80 patients (94.12%) had DCR (Table 2).

Comparison of Survival Analysis Between Groups

As of the last follow-up on June 15, 2024, the median follow-up duration was 15.9 months (95% CI:12.9–19.9) in the low-dose group and 14.3 months (95% CI:8.9–23.7) in the high-dose group (P = 0.390). Overall, 32 patients in the low-dose group and 22 patients in the high-dose experienced disease progression. There was no significant difference in PFS between the low-dose (mPFS, 9.4 months; 95% CI:6.9–13.8) and high-dose groups (mPFS, 10.5 months; 95% CI:7.9–17.1) (P = 0.837) (Figure 3A). Furthermore, PFS adjusted using IPTW also showed no significant difference between the low-dose and high-dose groups [mPFS: 11.8 months (95% CI:7.8–15.5) vs. 12.9 months (95% CI:7.9–NA),

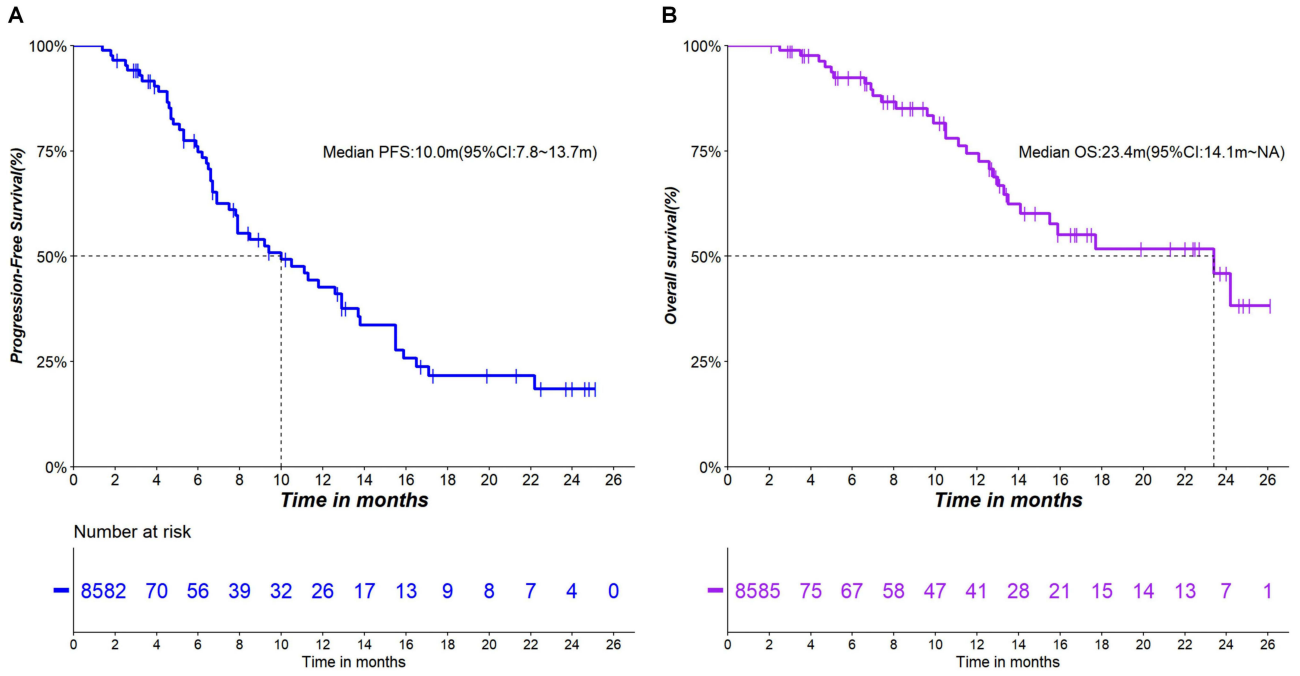

Figure 2 Survival outcomes of all patients. (**A**) Median progression-free survival (mPFS) for all patients was 10.0 months (95% CI: 7.8–13.7). (**B**) Median overall survival (mOS) for all patients was 23.4 months (95% CI: 14.1–NA).

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Table 2 Treatment Response in the Low-Dose and High-Dose Group Before IPTW

Best Response	RECIST 1.1, n (%)				mRECIST, n (%)			
	Total (n=85)	Low-Dose (n=47)	High-Dose (n=38)	*P* value	Total (n=85)	Low-Dose (n=47)	High-Dose (n=38)	*P* value
CR	1(1.18)	0(0.00)	1(2.63)	0.447	9(10.59)	4(8.51)	5(13.16)	0.505
PR	40(47.06)	21(44.68)	19(50.00)	0.625	44(51.76)	25(53.19)	19(50.00)	0.770
SD	39(45.88)	24(51.06)	15(39.47)	0.286	27(31.76)	16(34.04)	11(28.95)	0.616
PD	5(5.88)	2(4.26)	3(7.89)	0.652	5(5.88)	2(4.26)	3(7.89)	0.652
ORR	41(48.24)	21(44.68)	20(52.63)	0.466	53(62.35)	29(61.70)	24(63.16)	0.890
DCR	80(94.12)	45(95.74)	35(92.11)	0.806	80(94.12)	45(95.74)	35(92.11)	0.806

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; low-dose, Sintilimab plus 7.5 mg/Kg Bevacizumab; high-dose, Sintilimab plus 15 mg/Kg Bevacizumab.

P = 0.818] (Figure 3B). The PFS rates at 6/12/18 months also showed no significant differences either before or after IPTW adjustment (Figure 3A and B).

Nevertheless, the mOS in the low-dose group (23.4 months, 95% CI:14.1–NA) was numerically longer than that in the high-dose group (17.7 months, 95% CI:13.0–NA) before IPTW adjustment (P = 0.580) (Figure 4A). After IPTW adjustment, the corresponding mOS was 23.4 months (95% CI:15.5–NA) in the low-dose group and 24.2 months (95% CI: 13.5–NA) in the high-dose group (P = 0.908) (Figure 4B). The OS rates in the low-dose group were higher than those in the high-dose group both before (OS rate at 6/12/18 months: 94%/77%/55% vs. 91%/71%/48%) and after (OS rate at 6/12/18 months: 95%/82%/56% vs. 90%/77%/51%) IPTW adjustment (Figure 4A and B).

These results indicate that low-dose bevacizumab did not significantly shorten survival prolongation compared with the standard dose. The lack of survival disparity suggests that VEGF inhibition sufficient to support immunotherapy synergy may already be achieved at a dose of 7.5 mg/kg, and further dose escalation may not necessarily confer

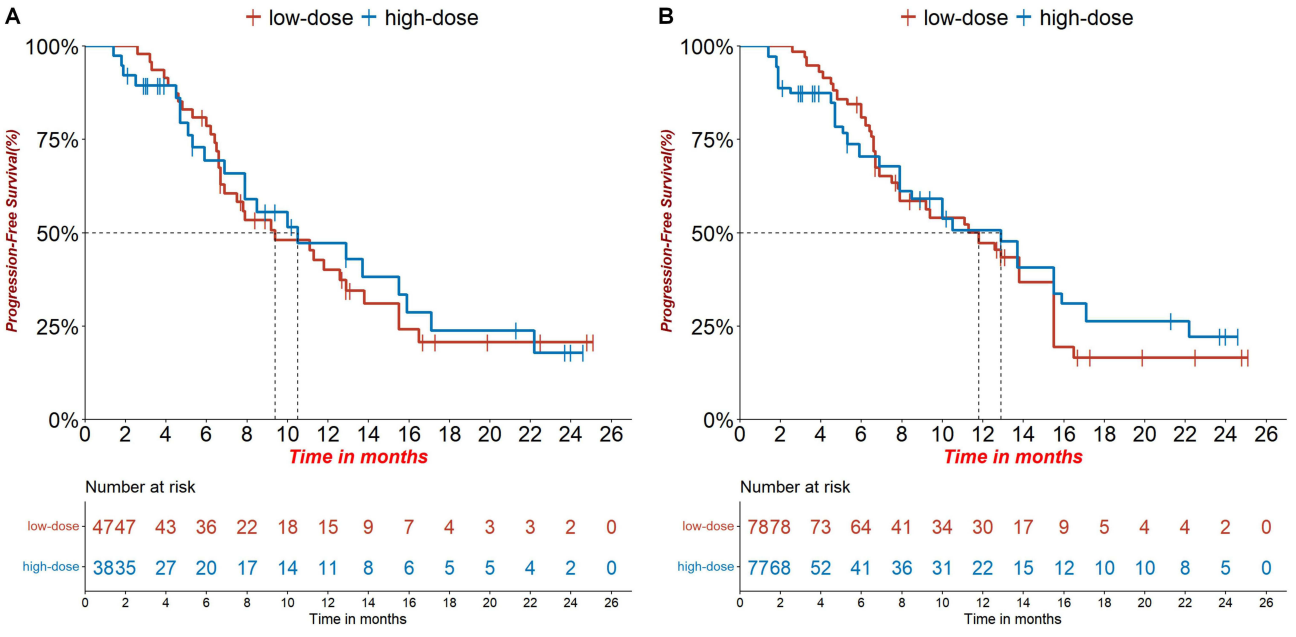

Figure 3 (**A**) Progression-free survival (PFS) and (**B**) PFS following adjustment using inverse probability of treatment weighting (IPTW) in the low-dose group and high-dose group. (**A**) Median progression-free survival (mPFS) for the low-dose group was 9.4 months (95% CI: 6.9–13.8) and for the high-dose group was 10.5 months (95% CI: 7.9–17.1) (P = 0.837), HR: 0.94 (95% CI:0.55–1.63), PFS rate at 6/12/18 months: 79%/40%/21% vs. 69%/47%/24%. (**B**) mPFS after adjustment using IPTW for the low-dose group was 11.8 months (95% CI:7.8–15.5) and for the high-dose group was 12.9 months (95% CI:7.9–NA) (P = 0.818), HR: 0.92 (95% CI:0.50–1.68), PFS rate at 6/12/18 months: 81%/47%/17% vs. 70%/51%/26%.

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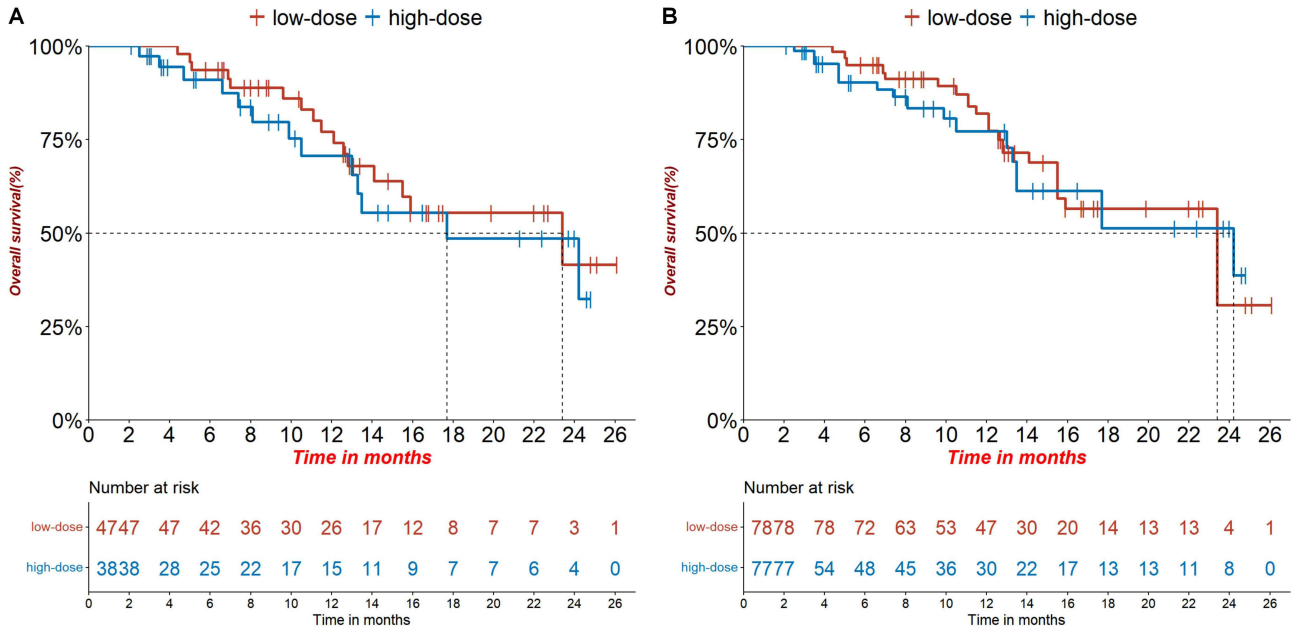

Figure 4 (**A**) Overall survival (OS) and (**B**) OS following adjustment using inverse probability of treatment weighting (IPTW) in the low-dose group and high-dose group. (**A**) Median overall survival (mOS) for the low-dose group was 23.4 months (95% CI: 14.1-NA) and for the high-dose group was 17.7 months (95% CI:13.0–NA) (P = 0.580), HR: 1.23 (95% CI:0.59–2.57), OS rate at 6/12/18 months: 94%/77%/55% vs. 91%/71%/48%. (**B**) mOS after adjustment using IPTW for the low-dose group was 23.4 months (95% CI:15.5–NA) and for the high-dose group was 24.2 months (95% CI: 13.5-NA) (P = 0.908), HR: 1.05 (95% CI:0.48–2.31), OS rate at 6/12/18 months: 95%/82%/56% vs. 90%/77%/51%.

additional survival benefit. In addition, improved tolerability in the low-dose group may have facilitated sustained treatment exposure, potentially offsetting theoretical pharmacodynamic advantage associated with higher dosing.

Comparison of Treatment Response Between Groups

Tumor responses prior to IPTW are summarized in Table 2. The best therapeutic response according to RECIST 1.1 was not significantly different between the low-dose and high-dose groups (CR:PR:SD:PD=0:21:24:2 vs. 1:19:15:3) (ORR=44.68% vs. 52.63%, P = 0.466), as well as those by mRECIST (CR:PR:SD:PD=4:25:16:2 vs. 5:19:11:3) (ORR=61.70% vs. 63.16%, P = 0.890). The DCR were 95.74% in the low-dose group and 92.11% in the high-dose group (P = 0.806) based on both RECIST and mRECIST criteria. Similarly, no significant differences in ORR or DCR were observed between the two groups after IPTW adjustment (Figure 5A–C).

Prognostic Factors Affecting PFS and OS

Before IPTW adjustment, univariate and multivariate Cox proportional hazards regression analyses were conducted to explore prognostic factors associated with PFS and OS (Figure 6). After balancing baseline covariates using IPTW, weighted Cox regression analyses were repeated to assess the stability of these associations (Figure 7).

Before IPTW, univariate analysis identified ECOG PS 1 score, AFP > 400 ng/mL, PVTT, and intrahepatic tumor number > 3 as significant predictors of shorter PFS. For OS, ECOG PS 1 score, AFP > 400 ng/mL, PVTT, and extrahepatic spread were associated with poorer prognosis; whereas treatment with TACE or TACE-HAIC were correlated with improved survival. Multivariate analysis confirmed ECOG PS 1 score and intrahepatic tumor number > 3 as independent predictors of worse PFS, while ECOG PS 1 score remained independently associated with shorter OS and TACE-HAIC was associated with improved OS.

After IPTW adjustment, multivariate analysis consistently identified ECOG PS 1 score and intrahepatic tumor number > 3 as independent predictors of worse PFS. ECOG PS 1 were also associated with poorer OS, whereas TACE-HAIC appeared to confer a survival benefit.

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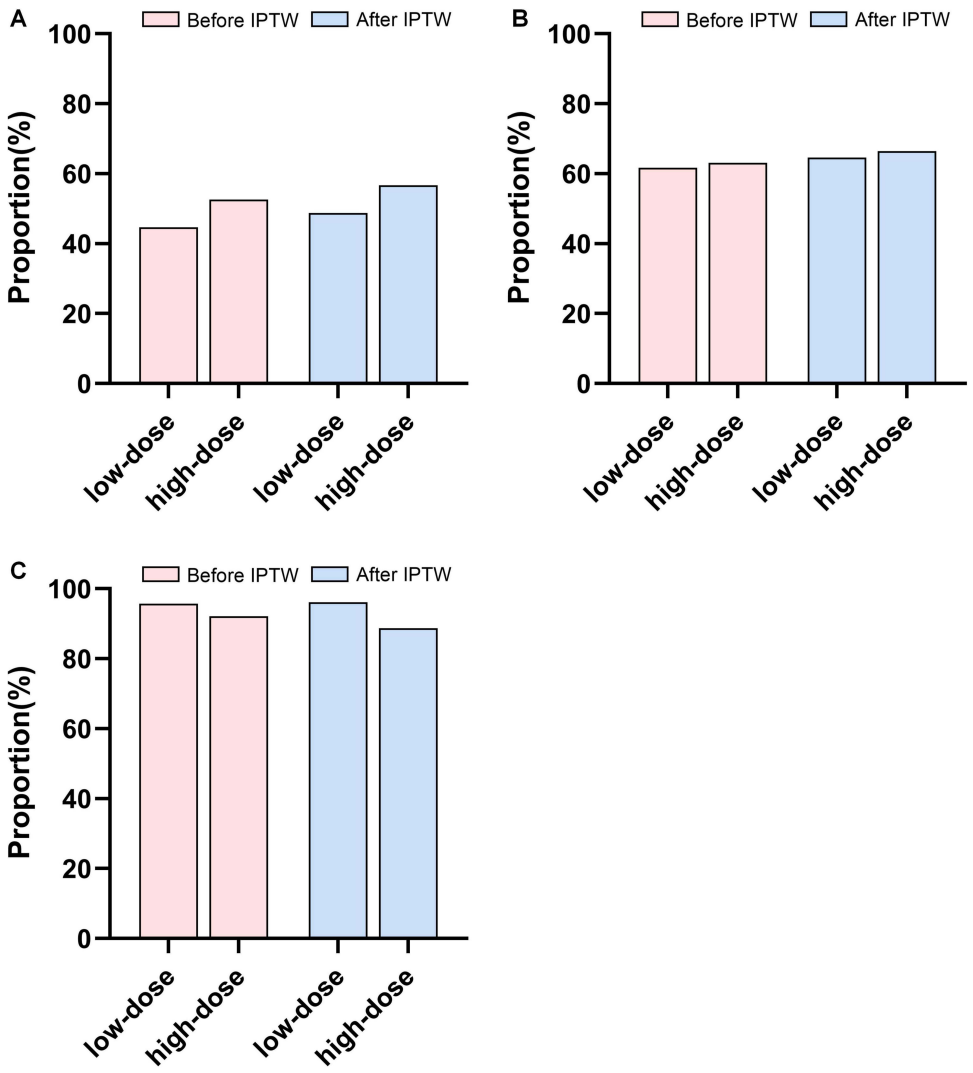

Figure 5 Comparison of treatment response between the low-dose group and the high-dose group before and after IPTW adjustment. (**A**) Bar plots of ORR assessed by RECIST 1.1 criteria. (**B**) Bar plots of ORR assessed by mRECIST criteria. (**C**) Bar plots of DCR assessed by RECIST 1.1 and mRECIST criteria.

Safety Analysis in the Low-Dose Group and High-Dose Group

TRAEs were summarized in Table 3. The most common AEs in both groups were TAT-related, including abdominal pain, fever, transient liver dysfunction (elevations in ALT, AST, and bilirubin), and chemotherapy-induced bone marrow suppression (leukopenia, neutropenia, and thrombocytopenia). No significant differences were observed between the two groups. All TAT-related AEs gradually resolved with symptomatic treatment, and no treatment-related deaths occurred.

Bleeding events were observed in 25 patients (29.41%). EGV bleeding occurred in 13 patients, including 5 (10.64%) in the low-dose group—3 (6.38%) with grade ≥ 3 bleeding and 2 (4.26%) with grade 1–2 bleeding—and 8 (21.05%) in the high-dose group—7 (18.42%) with grade ≥ 3 bleeding and 1 (2.63%) with grade 2 bleeding. The remaining 12 patients experienced grade 1–2 bleeding from other causes, including gastric ulcers, gingival bleeding, and epistaxis. Nine patients with EGV bleeding underwent successful endoscopic ligation or interventional embolization. However, four patients died from bleeding complications (one in the low-dose group and three in the high-dose group). Bevacizumab was permanently discontinued and the treatment regimen was modified after bleeding control in patients with grade ≥3 bleeding, whereas patients with grade 1–2 bleeding continued treatment, and no recurrent bleeding events were reported during subsequent therapy.

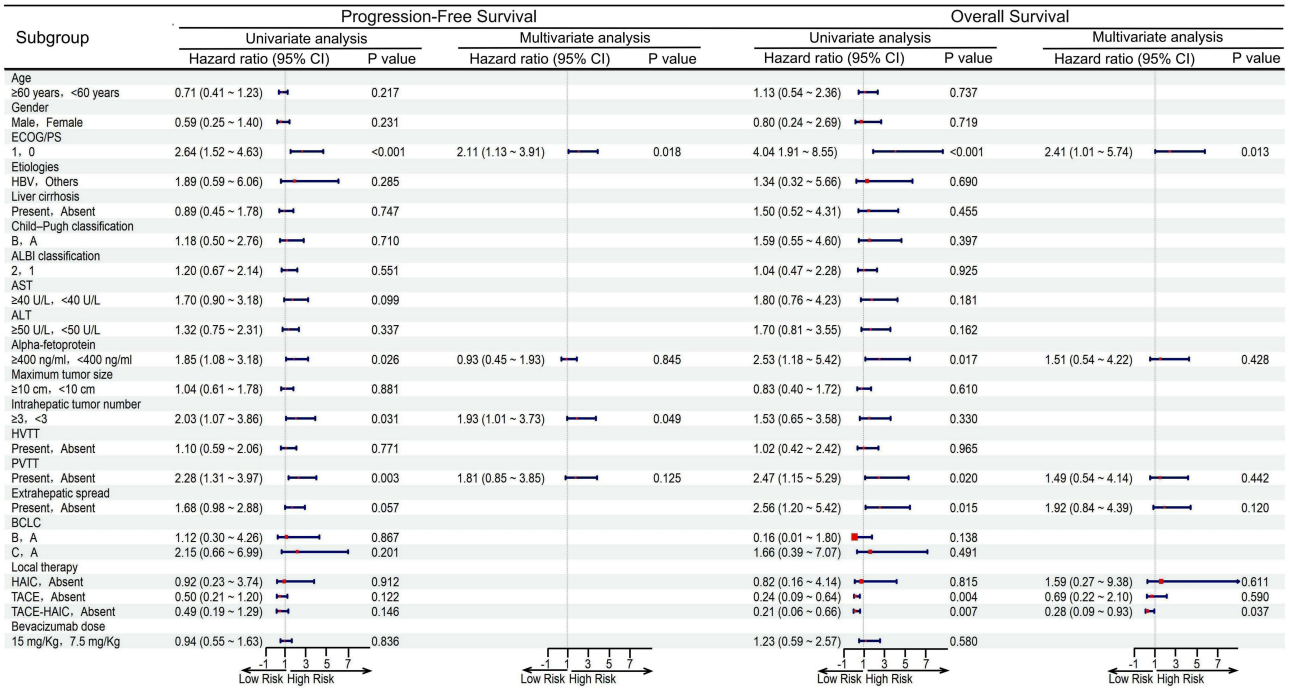

Figure 6 Forest plots of univariable and multivariable analyses for prognostic factors affecting PFS and OS before IPTW adjustment. Hazard ratios were estimated using Cox proportional hazards models. For categorical variables, the first category was defined as the reference group, and hazard ratios were calculated relative to that reference.

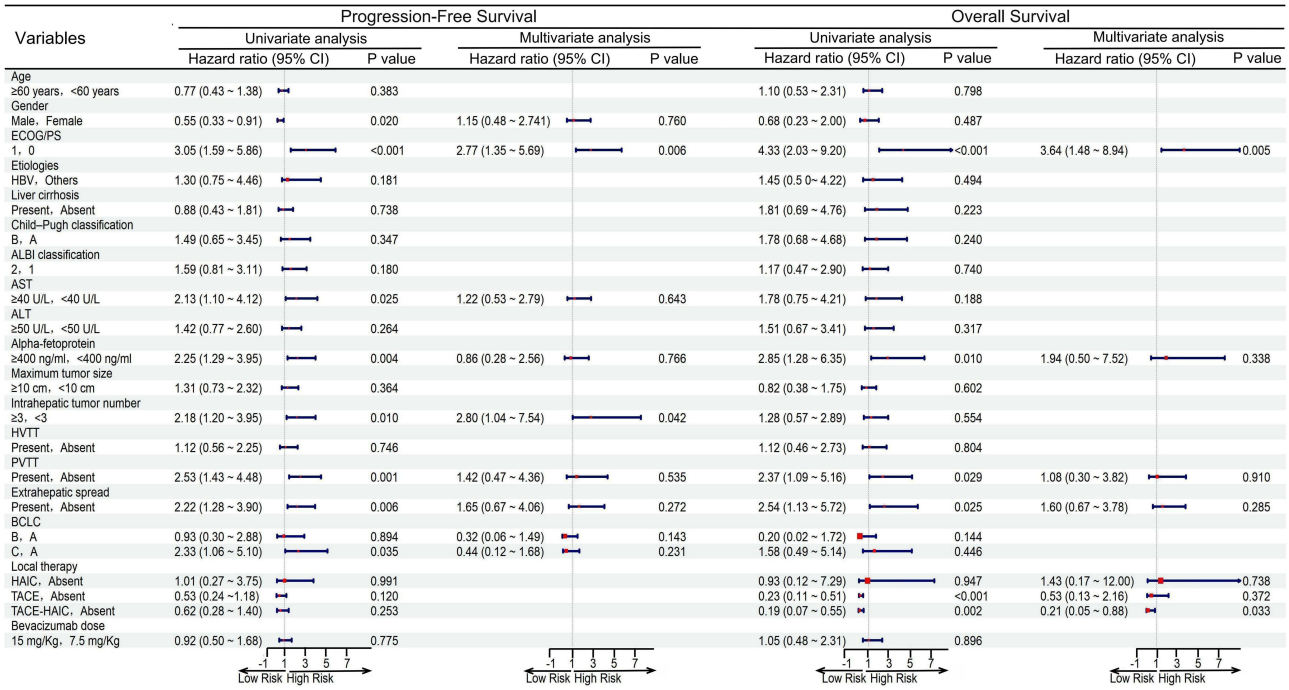

Figure 7 Forest plots of univariable and multivariable analyses for prognostic factors affecting PFS and OS after IPTW adjustment. Hazard ratios were estimated using Weighted Cox proportional hazards models. For categorical variables, the first category was defined as the reference group, and hazard ratios were calculated relative to that reference.

Comparison of Treatment Duration Between Groups

Sinti-Bev was interrupted or permanently discontinued for any reason in 32 patients (68.09%) in the low-dose group and in 21 patients (55.26%) in the high-dose group. In the low-dose group, five patients (15.62%)

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Table 3 Treatment-Related Adverse Events in the Low-Dose and High-Dose Group

Adverse Events	Any Grade, n (%)			Grades 1–2, n (%)			Grades 3–5, n (%)		
	Low-Dose (n=47)	High-Dose (n=38)	*P*	Low-Dose (n=47)	High-Dose (n=38)	*p*	Low-Dose (n=47)	High-Dose (n=38)	*P*
Hemorrhage	12(25.53)	13(34.21)	0.383	9(19.15)	6(15.79)	0.686	3(6.38)	7(18.42)	0.086
Esophageal–gastric varices bleeding	5(10.64)	8(21.05)	0.185	2(4.26)	1(2.63)	1.000	3(6.38)	7(18.42)	0.086
Hemorrhage from other body parts	7(14.89)	5(13.16)	0.819	7(14.89)	5(13.16)	0.819	0	0	0
Hypertension	13(27.66)	15(39.47)	0.249	12(25.53)	14(36.84)	0.261	1(2.13)	1(2.63)	1.000
Proteinuria	16(34.04)	15(39.47)	0.605	15(31.91)	13(34.21)	0.823	1(2.13)	2(5.26)	0.584
Hypothyroidism	11(23.40)	12(31.58)	0.399	11(23.40)	11(28.95)	0.562	0	1(2.63)	0.447
Hyperthyroidism	1(2.13)	2(5.26)	0.584	1(2.13)	2(5.26)	0.584	0	0	0
Rash	5(10.64)	7(18.42)	0.306	4(8.51)	6(15.79)	0.302	1(2.13)	1(2.63)	1.000
Itch	4(8.51)	5(13.16)	0.505	4(8.51)	5(13.16)	0.505	0	0	0
Leukopenia	18(38.30)	14(36.84)	0.890	16(34.04)	12(31.58)	0.810	2(4.26)	2(5.26)	1.000
Neutropenia	21(44.68)	17(44.74)	0.996	18(38.30)	15(39.47)	0.912	3(6.38)	2(5.26)	1.000
Thrombocytopenia	22(46.81)	18(47.37)	0.959	20(42.55)	15(39.47)	0.774	2(4.26)	3(7.89)	0.652
Aspartate aminotransferase increased	39(82.98)	31(81.58)	0.866	27(57.45)	21(55.26)	0.840	12(25.53)	10(26.31)	0.935
Alanine aminotransferase increased	37(78.72)	30(78.95)	0.980	28(59.57)	22(57.89)	0.876	9(19.15)	8(21.05)	0.827
Total bilirubin increased	26(55.32)	20(52.63)	0.805	26(55.32)	20(52.63)	0.805	0	0	0
Albumin decreased	24(51.06)	21(55.26)	0.700	24(51.06)	21(55.26)	0.700	0	0	0
Abdominal discomfort	34(72.34)	25(65.79)	0.515	32(68.09)	24(63.16)	0.634	2(4.26)	1(2.63)	1.000
Pyrexia	21(44.68)	17(44.74)	0.996	21(44.68)	16(42.11)	0.812	0	1(2.63)	0.447
Nausea and/or Vomiting	23(48.94)	19(50.00)	0.922	23(48.94)	19(50.00)	0.922	0	0	0
Fatigue	18(38.30)	15(39.47)	0.912	18(38.30)	15(39.47)	0.912	0	0	0
Decreased appetite	20(42.55)	16(42.11)	0.967	20(42.55)	16(42.11)	0.967	0	0	0
Diarrhea	5(10.64)	7(18.42)	0.306	5(10.64)	7(18.42)	0.306	0	0	0
Immune-related pneumonitis	1(2.13)	0	1.000	0	0	0	1(2.13)	0	1.000
Hand–foot skin reaction	1(2.13)	0	1.000	1(2.13)	0	1.000	0	0	0

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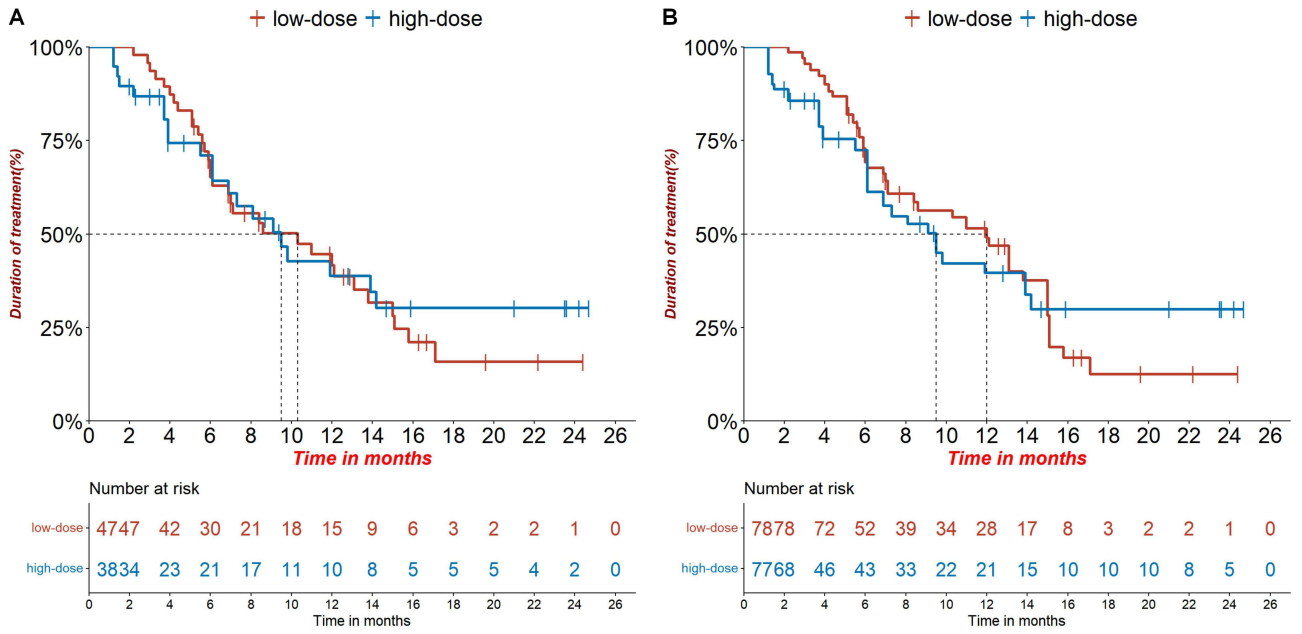

Figure 8 (**A**) Treatment duration and (**B**) treatment duration following adjustment using inverse probability of treatment weighting (IPTW) in the low-dose group and high-dose group. (**A**) Median treatment duration for the low-dose group was 10.3 months (95% CI:6.9–15.0) and for the high-dose group was 9.5 months (95% CI:6.1–NA) (P = 0.768). (**B**) Median treatment duration for the low-dose group was 12.0 months (95% CI:7.1–15.1) and for the high-dose group was 9.5 months (95% CI:6.1–NA) (P = 0.997).

discontinued due to AEs—including one case of interstitial pneumonia, one case of immunodermatitis, and three cases of bleeding—whereas the remaining patients discontinued due to PD or death. In contrast, nine patients (42.83%) discontinued treatment due to AEs in the high-dose group, including eight cases of bleeding (mainly EGV or gastric ulcer bleeding) and one case of proteinuria, while the remainder discontinued because of PD or death. Bleeding was the leading cause of Sinti-Bev discontinuation, accounting for 20.75% of treatment interruptions.

Further analysis revealed that the median treatment duration were 10.3 months in the low-dose group and 9.5 months in the high-dose group (Figure 8A). Post-IPTW analysis revealed that the median treatment duration in the low-dose group (12.0 months) was approximately 2.5 months longer than that in the high-dose group (9.5 months) (Figure 8B). Although this difference did not reach statistical significance, the numerically longer treatment duration in the low-dose group may reflect improved tolerability and reduced treatment discontinuation. Given that early interruption of bevacizumab has been associated with inferior survival outcomes in previous studies, the longer treatment exposure observed in the low-dose group may partly explain the lack of a significant difference in survival outcomes observed between the two dosing strategies.

Discussion

Based on the significant survival benefits demonstrated in the ORIENT-32 trial,[10] the Sinti-Bev regimen has been recommended by Chinese clinical guidelines as a first-line treatment for advanced HCC. However, the impact of bevacizumab dose on efficacy and safety remains controversial. A meta-analysis reported that atezolizumab combined with standard-dose bevacizumab produced superior tumor responses compared with low-dose regimens in advanced HCC.[29] In contrast, previous phase II studies demonstrated antitumor activity across various dosing schedules, although these results have not yet been validated in Phase III randomized trials.[23] Interestingly, earlier studies have shown that serum VEGF concentrations can be suppressed to undetectable levels with bevacizumab doses as low as 0.3 mg/kg, suggesting that higher doses may not provide additional dose-dependent antitumor benefits.[30] Therefore, it is crucial to further investigate the clinical efficacy and safety of low-dose bevacizumab combined with sintilimab in patients with uHCC.

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This study compared the efficacy of 7.5 mg/Kg and 15 mg/Kg bevacizumab in combination with sintilimab for uHCC. Overall treatment outcomes were significantly superior to those reported in the IMbrave150 trial and ORIENT-32 trial,[8,10] which may be attributed to the fact that 78 patients (91.76%) received TAT, consistent with real-world evidence showing enhanced efficacy of ICIs combined with bevacizumab and TAT.[11–13] Furthermore, the low-dose group did not demonstrate a significantly shorten PFS compared with high-dose group and achieved a comparable ORR. Notably, the mOS was numerically longer in the low-dose group, although the difference did not reach statistical significance. This trend may be related to the higher incidence of treatment interruption or mortality caused by TRAEs in the high-dose group. Similarly, a phase Ib trial reported no significant difference in tumor responses or survival outcomes between standard-dose and reduced-dose bevacizumab combined with sintilimab.[31] Another phase II study evaluating HAIC combined with sintilimab and 7.5 mg/Kg bevacizumab in uHCC reported a high ORR of 58.6% according to mRECIST criteria.[32] Moreover, several studies using 5–7.5 mg/kg bevacizumab in combination with atezolizumab have reported comparable efficacy to that observed in the IMbrave150 trial.[33–35] Collectively, low-dose bevacizumab may achieve tumor control and survival outcomes comparable to those of higher doses in patients with uHCC.

It is critical to maintain uninterrupted Sinti-Bev treatment for prolonging patient survival. Several studies have reported that treatment interruption is significantly associated with shorter OS and earlier disease progression, highlighting the importance of optimizing treatment management to avoid discontinuation of either agent.[25,36] In our study, the low-dose group demonstrated a longer median treatment duration, with the difference reaching approximately 2.5 months after IPTW adjustment. Additionally, patients in the low-dose group received more treatment cycles and experienced fewer TRAE-related treatment interruptions or deaths. Taken together, sintilimab combined with reduced-dose bevacizumab not only maintained antitumor activity and a more favorable safety profile, but also allowed longer treatment exposure. Therefore, bevacizumab dose reduction during treatment may represent a practical strategy to manage AEs while maintaining therapeutic benefit and treatment continuity in clinical practice.

Whether low-dose bevacizumab remains effective in HCC treatment continues to be a key clinical concern. Evidence from other malignancies suggests that low-dose bevacizumab can achieve comparable or even improved outcomes while reducing bevacizumab-related toxicity.[26,27] Beyond its anti-angiogenic activity, bevacizumab also exerts synergistic effects when combined with ICIs and/or TAT in HCC. First, bevacizumab may mitigate tumor recurrence and metastasis by counteracting VEGF upregulation induced by TAT.[37] Second, bevacizumab alleviates the VEGF-mediated immunosuppressive microenvironment and facilitates T-cell infiltration, thereby enhancing the efficacy of ICIs.[38] Additionally, bevacizumab promotes vascular normalization and improves tumor oxygenation, which facilitates more efficient delivery of chemotherapeutic agent and augments antitumor activity.[39,40] Notably, Sato et al[41] reported that even low-dose bevacizumab can effectively suppresses serum VEGF levels. Therefore, low-dose bevacizumab may still maintain its synergistic antitumor effects through adequately inhibiting VEGF expression. Furthermore, discontinuation of bevacizumab has been associated with a rebound increase in VEGF levels, potentially promoting tumor re-angiogenesis and progression. From this perspective, when high-dose bevacizumab is poorly tolerated, a reduced dose may represent an acceptable strategy to sustain VEGF suppression and delay tumor progression.

Long-term bevacizumab administration is associated with specific TRAEs, such as hypertension, proteinuria, and bleeding.[42] In the IMbrave150 trial, hypertension was generally managed with medication, whereas proteinuria was typically addressed by temporary treatment suspension, after which most patients resumed therapy.[8] Of greater concern, however, is the occurrence of bleeding. Although patients with untreated or inadequately treated EGV and a high bleeding risk were excluded from the IMbrave150 trial, the incidence of gastrointestinal bleeding remained higher in the Atezo-Bev group than in the sorafenib group (7% vs. 4.5%), particularly for acute variceal bleeding (AVB) related to PH (2.4% vs. 0.6%).[8] Similarly, the ORIENT-32 trial reported grade 3–5 bleeding events in 4.5% of patients receiving Sinti-Bev, predominantly involving the upper gastrointestinal bleeding (2.4%).[10] In contrast, REFLECT trial reported a lower incidence of EGV bleeding (1.47%) in patients treated with lenvatinib.[43] These findings suggest a higher bleeding risk associated with bevacizumab compared with tyrosine kinase inhibitors, and that the presence of EGV may further exacerbate this risk. In our study, 25 bleeding events (29.41%) were observed, including 13 cases of EGV bleeding, four of which resulted in death—substantially exceeding rates reported in previous studies. Grade ≥ 3 AVB occurred more frequently in the high-dose group. These results underscore the need for individualized dosing strategies in patients

unable to tolerate 15 mg/Kg bevacizumab, particularly those at elevated risk of gastrointestinal bleeding, such as individuals with EGV, thrombocytopenia, cardiovascular or cerebrovascular diseases, or advanced age. For such patients, low-dose bevacizumab may represent a more tolerable and potentially safer therapeutic alternative, while maintaining antitumor efficacy and improving treatment compliance and continuity.

This study has several limitations. First, its retrospective and observational design may introduce inherent selection bias and potential unmeasured confounding factors. Second, the relatively small sample size and the fact that the cohort predominantly consisted of HBV-related HCC patients from a single country limit the generalizability of these findings to the broader HCC population. Third, the follow-up duration may be insufficient to fully assess differences in OS between the two groups, and longer follow-up will be necessary to confirm the durability of survival outcomes. Finally, serum VEGF levels were not measured in this study; therefore, pharmacodynamic effects of bevacizumab were inferred from prior literature rather than directly assessed. Preclinical studies have shown that complete angiogenesis blockade induced by high-dose anti-VEGF therapy may worsen tumor hypoxia and promote an immunosuppressive microenvironment,[44,45] whereas lower doses may induce vascular normalization, improve tumor perfusion, and facilitate $CD8^+/CD4^+$ T-cell infiltration, thereby restoring a more immunosupportive tumor microenvironment.[44] Therefore, the efficacy and safety of low-dose bevacizumab should be further validated in prospective randomized studies with larger sample sizes.

Conclusion

In conclusion, sintilimab plus bevacizumab demonstrated promising antitumor activity in patients with uHCC. A lower bevacizumab dose (7.5 mg/kg) was associated with a more favorable safety profile without apparent compromise in efficacy, suggesting that it may serve as a suitable alternative for patients unable to tolerate standard-dose bevacizumab.

Abbreviations

HCC, hepatocellular carcinoma; uHCC, unresectable hepatocellular carcinoma; Sinti, Sintilimab; Atezo, atezolizumab; Bev, bevacizumab; Sinti-Bev, sintilimab plus bevacizumab; Atezo- Bev, atezolizumab plus bevacizumab; ICIs, immune checkpoint inhibitors; VEGF, Vascular endothelial growth factor; LC, liver cirrhosis; PH, portal hypertension; TAT, transarterial therapy; OS, overall survival; PFS, progression-free survival; AEs, adverse events; TRAEs, treatment-related adverse events; HBV, hepatitis B virus; IPTW, inverse probability of treatment weighting; EGV, esophagogastric varices; HVTT, hepatic vein tumor thrombus; PVTT, portal vein tumor thrombosis; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; DSA, digital subtraction angiography; CT, computed tomography; MRI, magnetic resonance imaging; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer; ALBI, Albumin-Bilirubin; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; HR, Hazard ratios; CI, confidence intervals.

Data Sharing Statement

The raw data supporting this study were derived from the electronic medical records of the Second Affiliated Hospital of Nanchang University, the First Affiliated Hospital of Gannan Medical University, and Ganzhou Fifth People's Hospital and are not publicly available due to patient privacy considerations and institutional data protection policies. De-identified data may be made available to qualified researchers upon reasonable request to the corresponding author, subject to approval by the relevant institutional ethics committees and data governance authorities.

Ethics Approval Statement

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University, China. Approval number: (2023)I– Medical Research Ethics Review (34).

Patient Consent Statement

The requirement for informed consent was waived by the institutional ethics committee, as the study involved no more than minimal risk to participants, and all data were fully anonymized prior to analysis.

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Author Contributions

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.

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Disclosure

All authors declare that they have no conflicts of interest and that no pharmaceutical company funding or financial relationships were involved in this study.

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