World Journal of Surgical Oncology

REVIEW

Open Access

Hepatic arterial infusion chemotherapy (HAIC) combined with sequential or concurrent systemic targeted immunotherapy for advanced hepatocellular carcinoma: a single-center retrospective study

Zheng Li[1], Miaogang Xiong[1], Yang Xiang[1], Gang Yang[1] and Yongfu Xiong[1*]

Abstract

Triple therapy of hepatic arterial infusion chemotherapy (HAIC) combined with immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs) achieves satisfactory clinical efficacy in advanced hepatocellular carcinoma (HCC). However, the optimal therapeutic strategy to improve prognosis in this patient population remains controversial. The objective of this retrospective study was to evaluate the efficacy and safety of HAIC-based therapy, either sequentially (SE) or concurrently (Con) combined with targeted immunotherapy, in patients with Barcelona Clinic Liver Cancer (BCLC) stage C HCC. This retrospective study analyzed 235 patients with advanced HCC who received FOLFOX-based HAIC in combination with ICIs and TKIs either concurrently or sequentially at the Affiliated Hospital of North Sichuan Medical College from January 2020 to December 2024. Propensity score matching (PSM) was performed at a 1:1 ratio to eliminate potential imbalances in confounding factors. Patients were categorized into the sequential group (SE) and concurrent group (Con) based on whether the interval between the completion of HAIC and the initiation of systemic therapy exceeded three weeks. Following PSM, each group contained 85 patients. Statistical comparisons of Overall Survival (OS) (via Kaplan-Meier and log-rank tests) revealed a significantly longer median survival in the Con group (14.5 months) versus the SE group (11.2 months, $P<0.01$). Furthermore, the median Progression-Free survival (PFS) in the Con group (7.9 months) was also longer than that in the SE group (6.2 months). Treatment responses and adverse events (AEs) profiles were documented. Upon analysis according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST), the objective response rate (ORR) of the SE regimen was lower than that of the Con regimen. The Con group had a generally higher AE incidence, with significantly higher rates of hyperbilirubinemia (44.7% vs. 24.7%, $p=0.04<0.05$) and anemia (43.5% vs. 16.5%, $p=0.005<0.05$) than the SE group. No grade 5 severe and life-threatening AEs were reported in either group.

*Correspondence:
Yongfu Xiong
Xiong-Yongfu@nsmc.edu.cn

Full list of author information is available at the end of the article

Keywords Hepatocellular carcinoma, Hepatic arterial infusion chemotherapy, Targeted therapy, Immunotherapy, Sequentially and concurrently

Introduction

Hepatocellular carcinoma (HCC) ranks as the seventh most prevalent cancer worldwide and the second leading cause of cancer-related deaths, its high mortality is closely linked to insidious disease progression and low rates of early diagnosis [1]. In China, approximately half of patients with HCC are diagnosed when the disease has progressed to the locally advanced stage, a phase often associated with vascular invasion (e.g., portal vein tumor thrombus). In this patient population, median survival is less than 5 months when supportive care is the only intervention provided, resulting in extremely poor clinical prognosis [2]. Despite advancements in systemic therapies (e.g., targeted agents and immune checkpoint inhibitors) in recent years, the objective response rate (ORR, For HCC, the metric is determined in accordance with the mRECIST criteria, representing the percentage of evaluable patients whose target lesions attain a status of complete response (CR) or partial response (PR).) of single-agent therapy remains low (e.g., sorafenib yields only 5.3%) [3]. Although combination strategies (e.g., atezolizumab plus bevacizumab) have improved efficacy, their ORR remains limited to approximately 30% [4, 5]. This fails to reach the widely recognized core ORR range of 35%–45%, which balances short-term efficacy and long-term survival, and thus cannot meet clinical needs [6, 7]. Therefore, exploring more effective treatment regimens is of critical importance.

In recent years, HAIC has demonstrated unique clinical value in the comprehensive management of advanced HCC. Compared with systemic chemotherapy, it directly targets the tumor-feeding arteries, significantly improving local tumor control rates while reducing systemic toxicities [8]. FOLFOX-HAIC serves as the core regimen for both systemic chemotherapy and HAIC combination chemotherapy in advanced HCC. Specifically, this regimen consists of HAIC combined with three core agents: oxaliplatin, leucovorin, and 5-fluorouracil (5-FU), which can elevate the ORR to a maximum of 35.4% [9, 10], representing a significant superiority over conventional systemic chemotherapy regimens. More notably, the combination of HAIC with systemic therapies (e.g., targeted agents or Programmed cell death protein 1/Programmed death-ligand 1(PD-1/PD-L1) inhibitors, a type of immune checkpoint inhibitor) can further increase ORR to 54.3%–65.9%, suggesting that the local treatment and systemic treatment may have a synergistic effect, prolonging the survival time of patients with advanced HCC [11, 12].

Over recent years, sequential therapy (SE) has shown potential in other malignancies, as staged drug administration may reduce toxicity while maintaining efficacy [13]. In the field of HCC, initial data implies that FOLFOX-HAIC may improve the anti-cancer efficacy of the combination of TKIs and PD-1/PD-L1 inhibitors; however, the optimal timing of combination (concurrent versus sequential) remains unclear. Additionally, for patients initially receiving HAIC monotherapy, whether sequential or concurrent administration of systemic therapy affects efficacy or increases the risk of adverse events remains undetermined. Thus, systematic evaluation of the efficacy and safety of sequential versus concurrent modalities of HAIC combined with systemic therapy is of great significance for optimizing clinical practice in advanced HCC.

This is a single-center retrospective study. The objective of this study is to compare the OS, PFS, and incidence of AEs between two administration modalities—concurrent (Con) and sequential (SE)—in patients with advanced HCC who received FOLFOX-HAIC combined with targeted agents and immunotherapeutic drugs at the Affiliated Hospital of North Sichuan Medical College (NSMC) between January 2020 and December 2024. Through this comparison, we aim to evaluate the efficacy and safety of the two modalities, thereby providing evidence-based support for the development of individualized treatment strategies.

Methods

Study design and patients

This retrospective study collected data from patients with intermediate to advanced HCC who were treated at the Affiliated Hospital of NSMC between January 2020 and December 2024. These patients received FOLFOX-HAIC treatment within the same treatment course, combined with ICIs and TKIs either concurrently or sequentially (Fig. 1). Participants in this analysis were required to meet these inclusion conditions: (1)Diagnosed with HCC by clinical or pathological criteria, with Barcelona Clinic Liver Cancer (BCLC) stage C; (2)Received triple therapy via sequential (SE) or Concurrent (Con) administration; (3) Completed at least 2 cycles of HAIC; (4) Child-Pugh class A or B; (5) Performance status score of 0 to 1 based on the Eastern Cooperative Oncology Group (ECOG) criteria; The exclusion criteria specified for this study are as follows: (1) HCC with concurrent other malignant tumors or severe systemic diseases; (2)Had previously received systemic therapies (including angiogenesis inhibitors and immunotherapy); (3) Patients who

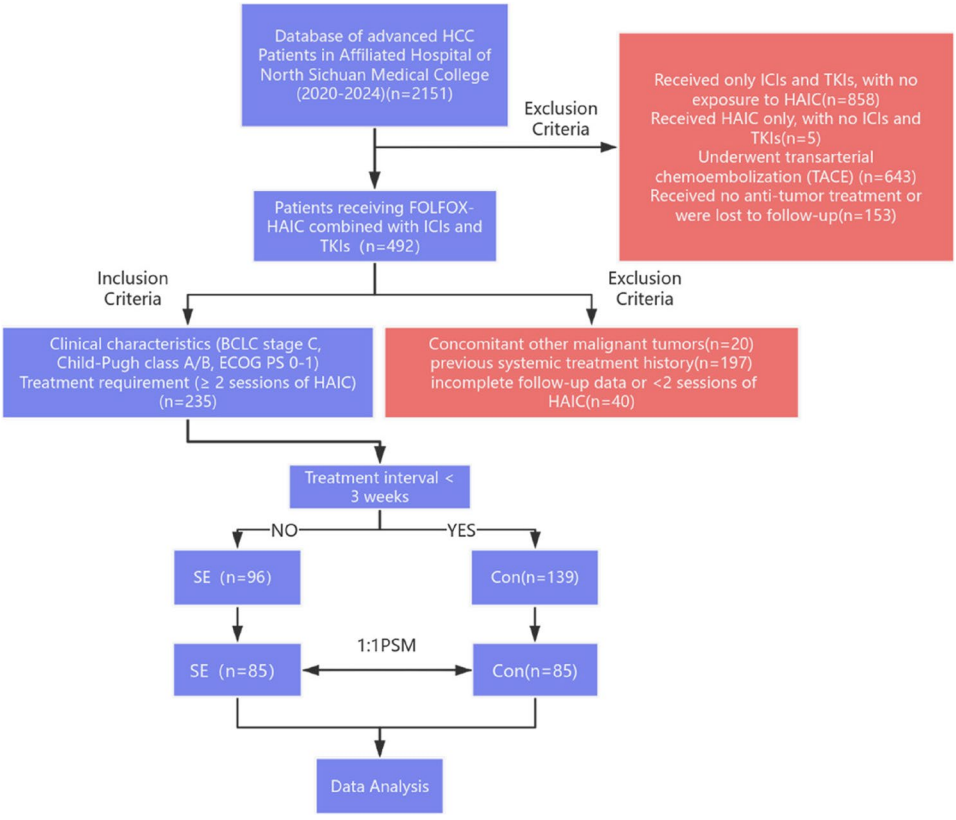


Fig. 1 Treatment Flowchart for Patients with BCLC Stage C HCC Receiving SE or Con

underwent transarterial chemoembolization (TACE); (4) Incompleteness existed in clinical or follow-up data.

All patients underwent 2–6 sessions of HAIC after initial admission, with an interval of approximately 3 weeks between treatments. Interventional radiologists performed hepatic artery catheterization under the guidance of digital subtraction angiography (DSA), followed by transcatheter HAIC after the procedure. In the routine surgical workflow, the operator performs selective catheterization of the celiac trunk, superior mesenteric artery, right inferior phrenic artery, and right renal artery using a 5 F RH puncture sheath for angiographic assessment, followed by precise cannulation of the tumor-feeding artery with a 2.2 F microcatheter. If angiography indicates that the tumor receives blood supply from multiple distinct vessels, the artery exhibiting denser staining in the tumor region, a perfusion range more closely matching the main tumor mass, and vascular branches that directly penetrate the tumor parenchyma on angiographic images is selected for targeted angiography within the suspected arterial branch. Based on the angiographic findings, the vessel is confirmed as the primary tumor-feeding artery, where a 2.2 F microcatheter is then indwelled. For the remaining feeding vessels, only embolization without chemotherapeutic agents is performed. Postoperatively, hepatic arterial infusion chemotherapy (HAIC) is administered via an infusion pump. The HAIC regimen administered via hepatic artery was as follows: Oxaliplatin: 85 mg/m² or 130 mg/m², administered via arterial infusion for 2–3 h. Leucovorin: 400 mg/m² or levoleucovorin 200 mg/m², administered via arterial infusion over 1–2 h. Fluorouracil (5-FU): 400 mg/m² given as an initial arterial bolus, followed by a continuous arterial infusion of 2400 mg/m² over 23–46 h [3]. All interventional procedures were performed by senior physicians with an academic rank of associate chief physician or above, each of whom had independently completed at least 50 cases of HAIC. A dedicated nursing team was assigned to provide full-process supportive care during the procedures. The criteria for determining technical success and failure were strictly predefined to ensure the objectivity and reproducibility of evaluations, with details as follows: Success Criteria: (1) The microcatheter was accurately and selectively cannulated into the main tumor-feeding artery with stable fixation and no procedural errors, ensuring that the drugs were directly delivered to the target region. (2) Angiography confirmed that the drugs were uniformly distributed within the tumor area, with no significant reflux into non-target blood vessels. (3) No severe interventional complications occurred during the operation, and no puncture-site issues requiring emergency intervention were observed

within 24 h after surgery. (4) The entire perfusion procedure was completed in accordance with the preset protocol, with no surgical interruption caused by equipment malfunctions or operational problems. Failure Criteria: (1) Accurate catheter placement could not be achieved due to vascular anatomical variations, inability to identify multiple feeding arteries, or other factors, resulting in the failure of targeted drug perfusion. (2) Severe drug reflux occurred or the perfusion failed to cover the main lesions, necessitating the interruption or modification of the protocol and leading to failure to achieve the expected drug concentration. (3) Severe adverse events such as vascular rupture with massive hemorrhage or fatal thrombosis occurred, requiring emergency termination of the operation for rescue. (4) The preset perfusion protocol was not completed due to non-technical factors, including equipment failure or unstable vital signs of the patient. The technical success rate of the interventional procedures exceeded 95%.

During the entire treatment cycle, patients who initiated systemic therapy less than 3 weeks after the first HAIC were assigned to the Con group; in contrast, patients who started the aforementioned systemic therapy more than 3 weeks after the completion of HAIC were categorized into the SE group. Treatment was continued until conversion to surgical intervention, occurrence of intolerable toxicity, or declaration of clinical death. The treatment frequency and duration of HAIC were individualized by physicians according to each patient's clinical evaluation. All small-molecule TKIs used in this study were administered in strict accordance with the specifications outlined in their respective official package inserts. Commonly prescribed oral TKIs included sorafenib, apatinib, lenvatinib, and donafenib, while bevacizumab was the primary intravenously administered agent. PD-1/PD-L1 inhibitors were all administered intravenously in strict compliance with the dosing recommendations in their package inserts, with a standard administration cycle of once every 3 weeks. Frequently used agents in this class included pembrolizumab, sintilimab, camrelizumab, tislelizumab, and atezolizumab. There is no conclusive evidence indicating differences in efficacy among different types of ICIs; therefore, the selection of such drugs is primarily determined by the attending physicians and the patients' economic status [14]. TKIs were administered in accordance with clinical practice guidelines [15].

Prior to the initiation of treatment, all patients and their families were fully informed about the treatment process and signed the informed consent form; after treatment, all patients also underwent regular assessments of treatment safety and therapeutic responses. The Institutional Review Board (IRB) of the Affiliated Hospital of NSMC has granted ethical approval for this research protocol(2025ER484-1). This study not only complies with the ethical standards established in the Declaration of Helsinki but also meets the reporting requirements for observational studies specified in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Assessment of clinical outcomes

We regularly evaluated patients' treatment efficacy and analyzed their tumor response status based on the mRECIST criteria, using the imaging data from patients' reexaminations (usually contrast-enhanced CT and contrast-enhanced MRI). The primary clinical endpoints were PFS and OS. In both patient groups, PFS was defined as the time from the first day of the patient's treatment initiation to the earliest occurrence of one of the following two events: 1.Radiological progression confirmed by imaging studies; 2.Patient death. OS was defined as the time interval from the initiation of triple therapy to the patient's death from any cause. The efficacy of hepatic tumors after treatment was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1), and classified into four categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) [16]. The secondary endpoints included the tumor's conversion resection rate (conversion rate), objective response rate (ORR), disease control rate (DCR), and treatment safety. During the treatment process, we continuously recorded treatment-related adverse events (TRAEs). For AEs emerging de novo during treatment, their categories and severity were classified and graded by integrating the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0) with the common complications of HAIC. Finally, statistical analyses were performed to determine whether there were statistically significant differences in these adverse events between the two patient groups.

Statistical analysis

For all clinical data in this study, researchers conducted statistical descriptions using the mean ± standard deviation, median (range), or number of cases (constituent ratio), respectively, based on the specific characteristics of the data. When conducting comparative analysis of the baseline characteristics between the two patient groups, the statistical methods were selected as follows: For continuously distributed variables, the independent samples t-test (Student's t-test) or Mann-Whitney U test was applied to analyze intergroup differences, depending on whether the data met prerequisites such as normal distribution. For categorical variables, the chi-square test (χ^2 test) or Fisher's exact test was used to evaluate intergroup distribution differences, based on the size

of theoretical frequencies.In the survival analysis section, the Kaplan-Meier method was employed to calculate patients' survival probabilities and generate survival curves. Meanwhile, the log-rank test was used to perform statistical testing on differences in survival outcomes between the two groups. In the matched samples, a univariate Cox regression model was first used to initially screen for potential risk factors that might affect patients' survival time. Subsequently, variables that reached the statistical significance level ($P < 0.05$) in the univariate analysis were included in a multivariate Cox regression model to control for the interference of confounding factors and further clarify the independent association between each variable and survival time. Additionally, to explore differences in the impact of treatment regimens on survival benefits, the study also used subgroup analysis to compare differences in OS between the two patient groups treated with different regimens. In addition, the χ^2 test was used to analyze the tumor efficacy between the two groups; the Kruskal-Wallis test was applied to evaluate the differences in adverse reactions between the two groups, which was further verified by the Mann-Whitney U test.

All statistical calculations in this study were performed using IBM SPSS Statistics software (Version 27.0). A two-tailed test was adopted for statistical testing, and a P-value < 0.05 was considered to indicate a statistically significant intergroup difference.

Results

Baseline clinical characteristics of patients

We collected information on patients with BCLC stage C HCC at the Affiliated Hospital of NSMC between January 2020 and December 2024. Among these patients, those who received HAIC combined with targeted immunotherapy were enrolled in the study and evaluated. Ultimately, a total of 235 participants were included in this study, with 96 in the SE group and 139 in the Con group. For a detailed overview of the baseline clinical characteristics of patients in both groups, refer to Table 1; in terms of age distribution, the mean age of patients in the SE group was 55.0 ± 11.3 years, while that in the Con group was 57.0 ± 13.5 years. Female patients accounted for 9 cases (9.3%) in the SE group and 17 cases (12.2%) in the Con group. All enrolled patients met the diagnostic criteria for BCLC stage C HCC and maintained ECOG PS scores < 2. In terms of treatment cycles, the median number of treatment cycles was 3 in the SE group versus 4 in the Con group. Specifically, 10 patients (10.4%) in the SE group completed more than 4 treatment cycles, while 31 patients (22.3%) in the Con group had more than 4 treatment cycles. This finding indicates that patients in the Con group received a greater number of treatments during the therapeutic course ($p = 0.018 < 0.05$). Comparative analysis revealed no statistically significant disparities ($P > 0.05$) in baseline demographic profiles, clinical parameters, or tumor features between treatment groups, demonstrating essential equivalence across measured variables. In this study, data were processed using a 1:1 PSM method. The factors incorporated into PSM—including patient age, gender, maximum tumor diameter, number of tumors, as well as vascular invasion and extrahepatic metastasis (EHM)—have either been used in clinical staging of liver cancer or confirmed as important indicators affecting the prognosis of patients with liver cancer [17]. After PSM, this study finally confirmed 85 patients in each group for analysis. No statistically significant differences were observed in most characteristics between the two groups ($P > 0.05$), with detailed data shown in Table 1. In terms of baseline information, the median age of patients was 55.4 years in the SE group and 55.6 years in the Con group. Regarding gender distribution, males accounted for 90.6% of patients in the SE group and 88.3% in the Con group. For tumor-related indicators, the maximum tumor diameter exceeded 10 cm in both groups, and the proportion of patients with multiple tumors was over 80% in each group. In terms of tumor progression characteristics, 65 patients (76.5%) in the SE group had vascular invasion, compared with 68 patients (80.0%) in the Con group. As for the occurrence of EHM, there were 11 cases (12.9%) in the SE group and 9 cases (11.6%) in the Con group. Notably, the median number of treatment cycles was 3 in the SE group, with 8 patients (9.4%) receiving more than 4 cycles of treatment; in the Con group, the median number of treatment cycles was 4, and 18 patients (21.2%) received more than 4 cycles. Consistent with the results before PSM, this finding indicates that patients in the Con group received a greater number of treatment cycles ($p = 0.033 < 0.05$). When completion of 4 treatment cycles was defined as the criterion for full-course treatment completion, the 4-cycle treatment completion rate in the SE group was less than 40%, whereas this rate reached 75.3% in the Con group.

Efficacy

The median OS was 11.3 months in the SE group and 14.9 months in the Con group (Fig. 2). After PSM, Kaplan-Meier analysis demonstrated significantly longer median OS in the Con group (14.5 months, 95% CI 13.0–15.8.0.8) versus SE group (11.2 months, 95% CI 9.0–11.8.0.8), with a statistically significant difference in OS between the two groups ($p = 0.03 < 0.05$). Survival rates at key timepoints favored Con therapy: 80.4% vs. 71.1% at 6 months, 54.8% vs. 45.0% at 12 months, and 26.2% vs. 11.1% at 24 months. Furthermore, A statistically significant difference in PFS was also observed between the two groups: among patients in the SE group who received the first course of

Table 1 Baseline clinical characteristics of patients

Factors	Before PSM			After PSM		
	SE(*N* = 96)	Con(*N* = 139)	*P*-value	SE(*N* = 85)	Con(*N* = 85)	*P*-value
Age						
Mean (SD)	55.0(11.3)	57.0(13.5)	0.766	55.2(11.2)	56.5(12.8)	0.955
Median [Min, Max]	55.0[30.0,77.0]	55.5[32.0,78.0]		55.4(30.0,77.0)	55.6(32.0,78.0)	
Sex						
Female	9(9.3%)	17(12.2%)	0.493	8(9.4%)	10(11.7%)	0.624
Male	87(90.7%)	122(87.8%)		77(90.6%)	75(88.3%)	
HAIC circles						
> 4	10(10.4%)	31(22.3%)	0.018	8(9.4%)	18(21.2%)	0.033
≤ 4	86(89.6%)	108(77.7%)		77(90.6%)	67(78.8%)	
ECOG PS						
0–1	96(100%)	139(100%)	1	85(100%)	85(100%)	1
Hepatitis B virus						
Negative	25(26.0%)	28(20.1%)	0.288	20(23.5%)	21(24.7%)	0.858
Positive	71(74.0%)	111(79.9%)		65(76.5%)	64(75.3%)	
Child–Pugh						
A	86(89.6%)	128(92.8%)	0.512	78(91.7%)	79(92.4%)	0.774
B	10(10.4%)	11(7.2%)		7(8.3%)	6(7.6%)	
AFP > 400 ng/mL						
No	25(26.0%)	30(21.6%)	0.424	21(25.0%)	19(22.4%)	0.718
YES	71(74.0%)	109(78.4%)		64(75.0%)	66(77.6%)	
Maximum tumor diameter						
Mean (SD)	9.9(2.95)	9.9(3.58)	0.752	10.1(2.94)	10.2(2.66)	0.568
Median [Min, Max]	10.1(2.4,16.0)	10.0(2.5,20.0)		10.2(2.4,16.0)	10.1(3.5,19.1)	
Tumor number						
Single	16(16.7%)	25(18.0%)	0.793	12(14.1%)	15(17.6%)	0.529
Multiple	80(83.33%)	114(82.0%)		73(85.9%)	70(82.4%)	
Vascular invasion						
NO	23(24.0%)	31(22.3%)	0.764	20(23.5%)	17(20.0%)	0.576
YES	73(76.0%)	108(77.6%)		65(76.5%)	68(80.0%)	
Extrahepatic metastasis						
NO	81(84.3%)	123(88.5%)	0.357	74(87.1%)	76(89.4%)	0.634
YES	15(15.7%)	16(11.5%)		11(12.9%)	9(11.6%)	
BCLC						
C	96(100%)	139(100%)	1	85(100%)	85(100%)	1

triple therapy, 23 cases developed disease progression; in contrast, only 12 cases in the Con group experienced disease progression($p = 0.039 < 0.05$), the median PFS in the Con group (7.9 months) was also longer than that in the SE group (6.2 months), 10 patients in the Con group achieved downstaging and underwent conversion resection, in contrast to only 1 patient in the SE group. Data showed that the Con group had superior ORR and DCR. Further stratified analysis revealed that the proportion of patients achieving CR was significantly higher in the Con group, whereas the proportion of patients with PD was notably lower, with all the aforementioned differences reaching statistical significance ($P < 0.01$) (Table 2).

Several factors were found to potentially affect OS, including the SE regimen [hazard ratio (HR): 1.33; 95% CI (1.17, 1.55)], Child-Pugh class B [HR: 2.4; 95% CI (1.60, 3.60)], maximum tumor diameter [HR: 1.15; 95% CI (1.05, 1.25)], AFP levels exceeding 400 mg/mL [HR: 1.30; 95% CI (1.15, 1.60)], and multiple tumors [HR: 1.50; 95% CI (1.20, 1.85)] (Fig. 3A). In the multivariate Cox regression analysis, the Con group showed a reduced mortality risk in comparison to the SE group [HR: 0.7; 95% CI (0.58, 0.89)]. Additionally, Child-Pugh class B [HR: 2.5; 95% CI (2.20, 2.65)] and tumor count [HR: 1.27; 95% CI (1.04, 1.45)] were confirmed as independent prognostic indicators for OS (Fig. 3B).

Subgroup Cox analysis demonstrated superior survival outcomes (lower HRs) for Con therapy across specific patient populations, including males, patients aged < 60 years, those receiving > 4 HAIC cycles, hepatitis B carriers, individuals with AFP < 400 ng/mL, Child-Pugh A patients, and those with solitary tumors, vascular invasion, or localized disease (Fig. 4)..

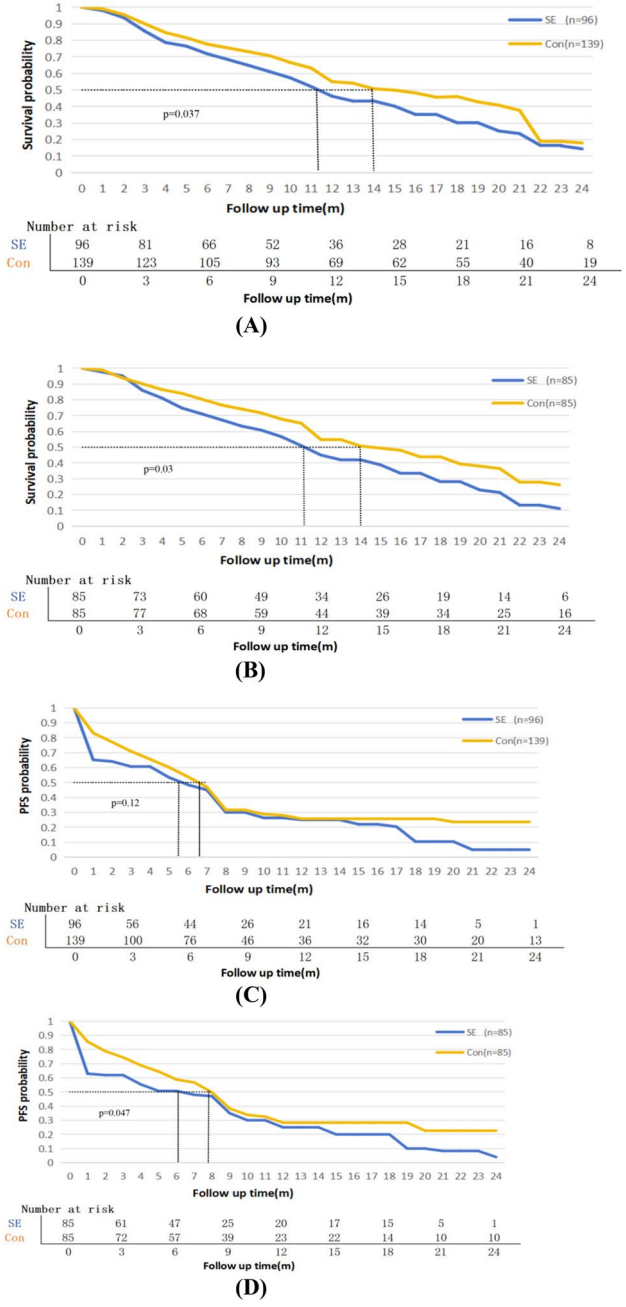


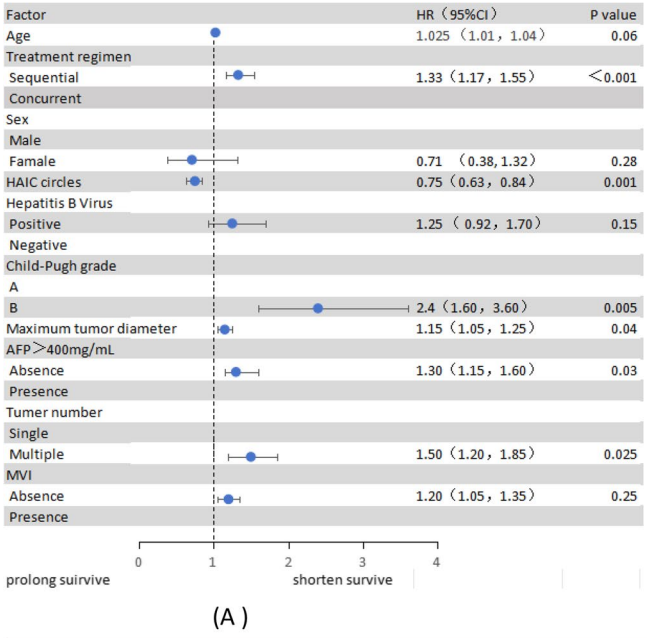
Fig. 2 Comparison of OS and PFS Between the Two Groups via the Kaplan-Meier analysis: Figure **A** and Figure **C** depict the OS and PFS results before PSM, respectively; Figure **B** and Figure **D** depict the OS and PFS results after PSM, respectively

Table 2 Objective tumor response assessment by mRECIST criteria following PSM

	SE	Con	*P* value
CR	1(1.2%)	10(11.8%)	< 0.01
PR	28(32.9%)	39(45.9%)	0.09
SD	26(30.6%)	23(27.0%)	0.60
PD	30(35.3%)	13(15.3%)	< 0.01

Safety

The results indicated that after the completion of PSM, the Con group exhibited a higher incidence of AEs. In both groups, more than 80% of patients developed abdominal pain of varying severity after initiating HAIC, particularly during oxaliplatin infusion. For this condition, substantial relief is usually achieved by adjusting the infusion rate or administering spasmolytic agents and analgesics, with very few patients discontinuing treatment due to pain. Due to the use of chemotherapeutic agents, Nausea was a frequent AE in both groups, with an incidence of 58.8% (50/85) in the SE group and 64.7% (55/85) in the Con group, it was usually addressed symptomatically with 5-HT receptor antagonists. Both groups also exhibited a high incidence of hand-foot syndrome(HFS) [SE: 32.9% (28/85); Con: 45.9% (39/85)], which generally resolved with symptomatic treatment and health education. In both groups, elevations in liver injury indicators were the most intuitive manifestation of HAIC-induced hepatotoxicity and also the most common grade 3–4 AEs, specifically including increased aspartate transaminase (AST) levels [SE group: 62.4% (53/85); Con group: 69.4% (39/85)] and elevated alanine transaminase (ALT) levels [SE group: 68.2% (58/85); Con group: 71.8% (61/85)]. The primary cause of these indicator elevations is the direct hepatocellular damage induced by oxaliplatin and fluorouracil. Additionally, patients with HCC are often complicated with liver cirrhosis or chronic hepatitis, which results in impaired hepatic regenerative capacity as well as weakened detoxification and metabolic functions. Most cases of mild liver injury can be alleviated by adjusting drug doses and administering hepatoprotective agents, and the indicators usually return to normal within 3 weeks. The Con group had a higher incidence of anemia, agranulocytosis, and thrombocytopenia. This phenomenon was attributed to two factors: on one hand, it was caused by hypersplenism secondary to liver cirrhosis; on the other hand, it resulted from bone marrow suppression induced by chemotherapy drugs. Typically, patients' indices could return to normal after symptomatic treatment. Biliary sclerosis is one of the common complications after HAIC. In the present study, no severe biliary sclerosis occurred in either group: 24.7% (21/85) of patients in the SE group and 28.2% (24/85) in the Con group exhibited mild elevations in alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), total bilirubin (TBIL), and direct bilirubin (DBIL). Most of these patients had their indices normalized within one month after symptomatic treatment. In HAIC, failures of catheters and infusion pumps may not only interrupt treatment but also trigger severe complications (such as liver injury and local thrombosis) due to abnormal drug dosages or extravasation. Among these issues, catheter occlusion is the most common cause, which results from



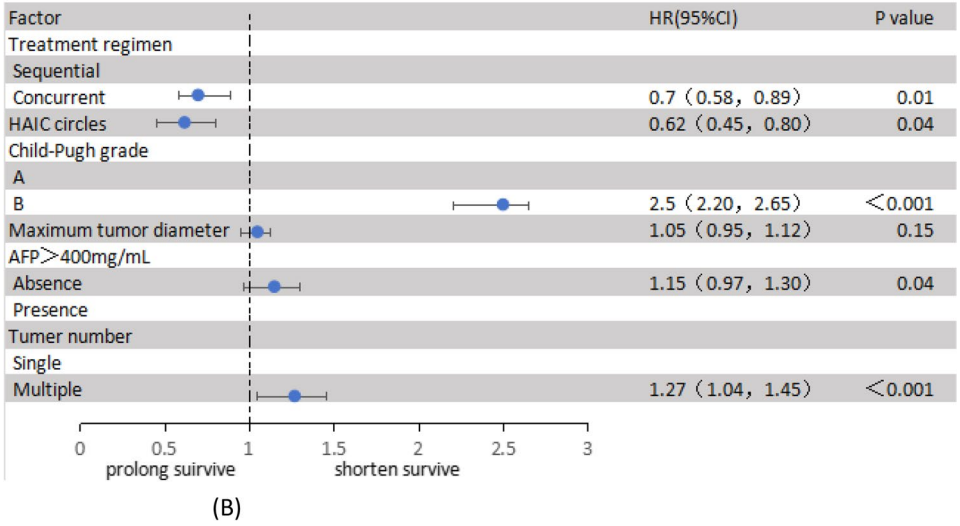


Fig. 3 Cox regression analyses of OS: (**A**) univariate and (**B**) multivariate. AFP: alpha-fetoprotein; MVI · macrovascular invasion; EHM · extrahepatic metastasis

excessively high concentrations of chemotherapeutic agents, excessively slow infusion rates, or intravascular blood coagulation within the catheter. Fortunately, these problems are all preventable. No such adverse events were observed in this study, though this may also be attributed to the small sample size of cases enrolled in the research. Postoperative infection is one of the non-negligible complications, with fever being its most common manifestation. In the SE group, 10.6% (9/85) of patients were considered to have postoperative infection, compared with 14.1% (14/85) in the Con group. In clinical practice, the incidence and severity of infection can be effectively reduced through strict aseptic techniques, enhanced catheter/puncture site care, individualized assessment of patients' infection risk (e.g., correction of hypoalbuminemia and blood glucose control before surgery), and management of myelosuppression.

No severe (grade 5) AEs occurred in either treatment arm. In comparison, the Con group had a higher overall incidence of adverse reactions; notably, statistically significant differences were detected in the incidence rates of hyperbilirubinemia ($p = 0.04 < 0.05$) and anemia ($p = 0.005 < 0.05$) between the two groups. Nevertheless, the severity of these events was generally mild, and most patients recovered to normal conditions following corresponding treatment. All adverse events were manageable and tolerable (Table 3).

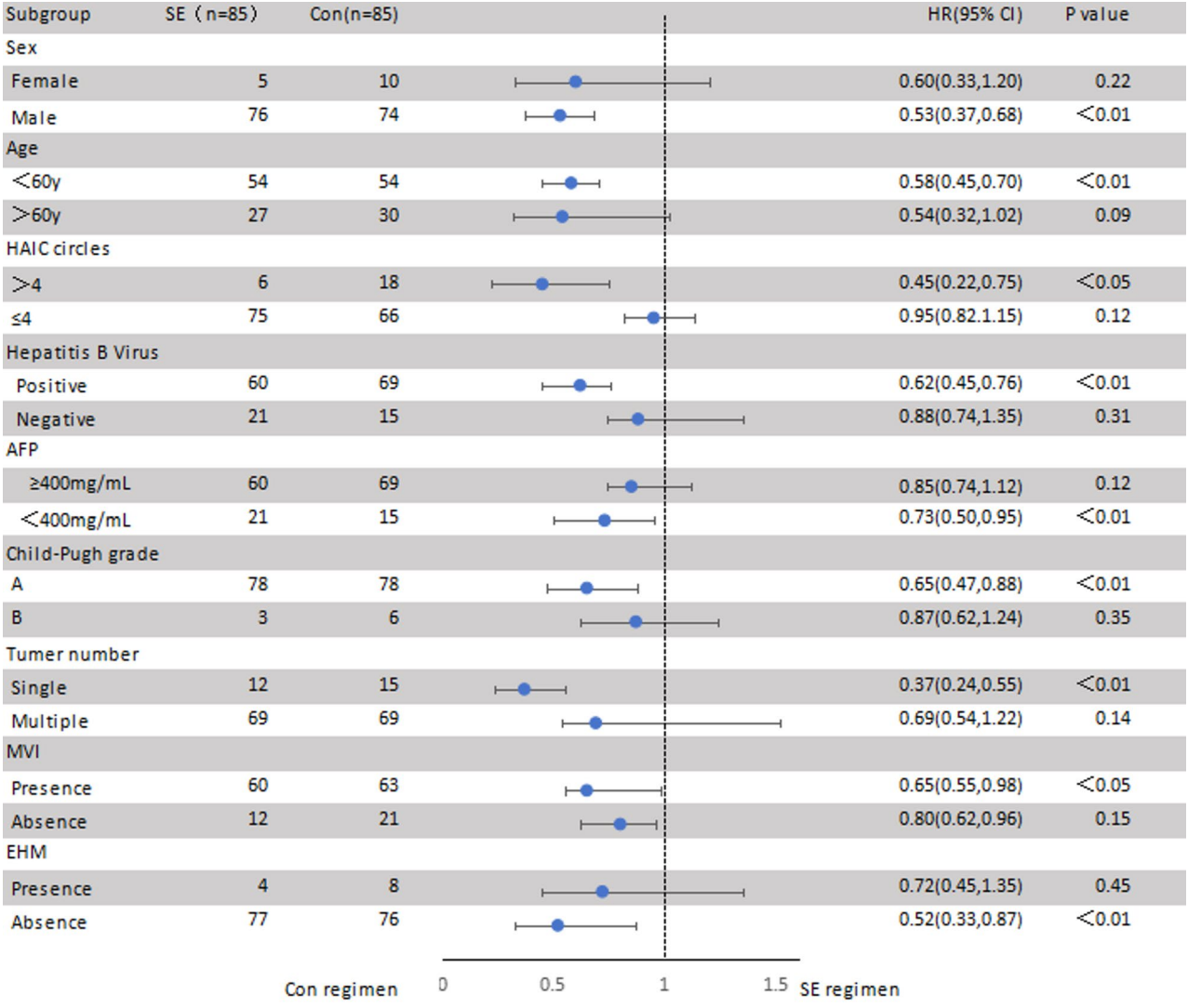


Fig. 4 OS subgroup comparisons for Con versus SE treatment modalities

Discussion

For advanced unresectable HCC, the triple therapy regimen based on HAIC, in combination with targeted therapy and immunotherapy, has been widely applied in clinical practice, and its efficacy has been validated [18]; however, the optimal administration strategy for this triple therapy—whether concurrent or sequential dosing—remains an urgent clinical problem to be addressed. In combination therapies for other cancer types, numerous studies have utilized the sequential (SE) and concurrent (Con) approaches [13, 19]. Based on the data of this study and relevant literature [20–22], we propose that Con may prolong patients' survival when adverse reactions are tolerable. This retrospective single-center study evaluates the effectiveness and safety of triple therapy in advanced HCC patients. The findings demonstrate that Con therapy significantly improves OS and PFS, along with a superior ORR. Both univariate and multivariate analyses identified Con therapy as an independent prognostic factor for improved survival. Furthermore, subgroup analysis confirmed the superior efficacy of Con-based triple therapy compared to SE-based treatment.

Additionally, after PSM, the results showed that the median OS and PFS in the Con group were longer than those in the SE group. Specifically, the median OS was 14.5 months (95% CI: 13.0–15.8) in the Con group versus 11.2 months (95% CI: 9.0–11.8) in the SE group; furthermore, 10 patients in the Con group achieved CR, compared with only 1 patient in the SE group ($p < 0.01$). Meanwhile, 10 patients in the Con group achieved tumor downstaging following combined therapy and underwent second-stage surgical resection after rigorous preoperative evaluation, among whom 7 received laparoscopic hepatectomy and 3 underwent open hepatectomy. In contrast, only 1 patient in the SE group underwent laparoscopic hepatectomy for HCC. A surgical margin of

Table 3 Analysis of complications in SE versus Con therapy groups following PSM

N(%)	Sequential(*n* = 85)			Concurrent(*n* = 85)			*P*-value
	Grade1–2	Grade3–4	Total	Grade1–2	Grade333–4	Total	
Fever	8(9.4%)	1(1.2%)	9(10.6%)	10(11.8%)	2(2.4%)	12(14.1%)	0.32
Nausea	46(54.1%)	4(4.7%)	50(58.8%)	50(58.8%)	5(5.9%)	55(64.7%)	0.47
Vomit	29(34.1%)	2(2.4%)	31(36.5%)	35(41.2%)	3(3.5%)	38(44.7%)	0.38
Abdominal pain	60(70.6%)	12(14.1%)	72(84.7%)	63(74.1%)	14(16.5%)	77(90.6%)	0.50
Elevated ALT	36(42.4%)	22(25.9%)	58(68.2%)	40(47.1%)	21(24.7%)	61(71.8%)	0.74
Elevated AST	28(32.9%)	25(29.4%)	53(62.4%)	35(41.2%)	24(28.2%)	59(69.4%)	0.50
Hyperbilirubinemia	20(23.5%)	1(1.2%)	21(24.7%)	35(41.2%)	3(3.5%)	38(44.7%)	0.04
Anemia	12(14.1%)	2(2.4%)	14(16.5%)	33(38.8%)	4(4.7%)	37(43.5%)	0.005
Neutropenia	33(38.8%)	5(5.9%)	38(44.7%)	45(52.9%)	6(7.1%)	51(60.0%)	0.10
Thrombocytopenia	28(32.9%)	1(1.2%)	29(34.1%)	33(38.8%)	2(2.4%)	35(41.2%)	0.51
Bleeding	3(3.5%)	0	3(3.5%)	5(5.9%)	1(1.2%)	6(7.1%)	0.48
Diarrhea	24(28.2%)	3(3.5%)	27(31.8%)	20(23.5%)	2(2.4%)	22(25.9%)	0.60
Hoarseness	6(7.1%)	0	6(7.1%)	5(5.9%)	0	5(5.9%)	0.81
Rash	13(15.3%)	1(1.2%)	14(16.5%)	24(28.2%)	3(3.5%)	27(31.8%)	0.07
Hand–foot syndrome	26(30.6%)	2(2.4%)	28(32.9%)	36(42.4%)	3(3.5%)	39(45.9%)	0.18
Hpertension	15(17.6%)	1(1.2%)	16(18.8%)	18(21.2%)	0	18(21.2%)	0.72
RCCEP	26(30.6%)	2(2.4%)	28(32.9%)	30(35.3%)	3(3.5%)	33(38.8%)	0.52
Hypothyroidism	11(12.9%)	0	11(12.9%)	12(14.1%)	0	12(14.1%)	0.81
Fatigue	11(12.9%)	0	11(12.9%)	14(16.5%)	1(1.2%)	15(17.6%)	0.40
Hepatitis	0	0	0	0	0	0	1
Pneumonia	0	0	0	0	0	0	1
Proteinuria	33(38.8%)	2(2.4%)	35(41.2%)	29(34.1%)	4(4.7%)	33(38.8%)	
Hepatic encephalopathy	0	0	0	0	0	0	1
biliary sclerosis	21(24.7%)	0	21(24.7%)	24(28.2%)	0	24(28.2%)	0.61
catheter/pump failure	0	0	0	0	0	0	1
infections	9(10.6%)	0	9(10.6%)	12(14.1%)	0	12(14.1%)	1

RCCEP, reactive cutaneous capillary endothelial proliferation

at least 1 cm was strictly ensured for all resected cases. For patients with vascular invasion, the involved vascular segments were resected to guarantee the absence of tumor thrombus in the resected vascular margins. For patients with confirmed oligometastasis on preoperative evaluation, synchronous surgical resection or ablation of metastatic lesions was performed only after the metastatic foci had achieved CR. Postoperative pathological examination confirmed negative tumor cell status in all surgical margins. Patients who underwent surgical resection in this study exhibited superior tumor control efficacy with the HAIC-based triple therapy regimen. As the cornerstone of curative treatment for HCC, surgical resection enables complete eradication of tumor lesions, thereby reducing tumor burden at the source and conferring substantial benefits on the long-term prognosis of HCC patients. These findings suggest that patients in the Con group may have a more favorable prognosis, indicating that the concurrent administration regimen could accelerate tumor regression and achieve a deeper level of remission. In the present study, the concurrent administration regimen achieved a remarkably high ORR of 57.6%, which was significantly superior to that of single-agent targeted therapy (e.g., sorafenib, with an ORR of only 5.3%), FOLFOX-based HAIC (with a maximum ORR of 35.4%), and other combination therapies (e.g., atezolizumab plus bevacizumab, with an ORR of less than 30%; pembrolizumab plus lenvatinib, with an ORR of 40.8%; and camrelizumab plus rivoceranib, with an ORR of 33.1%) [3–5, 7, 9, 10, 23].

Univariate analysis identified several prognostic factors for OS, including: SE treatment regimen [HR: 1.33, 95%CI (1.17–1.55)], Child-Pugh B classification [HR: 2.4, 95%CI (1.60–3.60)], larger tumor diameter [HR: 1.15, 95%CI (1.05–1.25)], elevated AFP > 400 mg/mL [HR: 1.30, 95%CI (1.15–1.60)], and multifocal lesions [HR: 1.50, 95%CI (1.20–1.85)]. Subsequent multivariate Cox regression demonstrated superior survival outcomes with Con therapy versus SE [HR = 0.7, 95%CI (0.58–0.89)], with Child-Pugh B status [HR: 2.5, 95%CI (2.20–2.65)] and tumor multiplicity [HR: 1.27, 95%CI (1.04–1.45)] remaining independent predictors. Subgroup survival analysis demonstrated superior tumor response with the Con protocol specifically in HBV-associated HCC cases presenting with solitary lesions, vascular invasion but without EHM. These findings suggest the Con approach potentiates the therapeutic synergy between molecular-targeted agents and immunomodulators, establishing its

preferential clinical utility over sequential therapy for advanced-stage HCC.

HAIC destroys tumor-feeding arteries via local high-concentration drug delivery, kills tumor cells, releases tumor-associated antigens, and converts "cold tumors" into "hot tumors". ICIs can facilitate the transition of the tumor microenvironment from an "immunosuppressive state" to an "immune-activated state", and this facilitative effect is more prominently manifested in "hot tumors" [24]. Studies have shown that active angiogenesis in solid tumors is often associated with poor prognosis, and vascular normalization helps improve the efficacy of ICIs and chemotherapy. Additionally, concurrent therapy can induce tumor necrosis or rapid tumor shrinkage, reduce hepatic tumor burden, and further prolong patient survival [5, 25]. Therefore, these findings suggest that Con delivery of HAIC, angiogenesis inhibitors, and ICIs may offer superior therapeutic benefits. Conversely, if the interval between HAIC and systemic therapy is excessively prolonged, it may not only substantially reduce or even deplete the immune cells recruited within the tumor through multiple pathways, but also accelerate the formation process of new tumor-feeding microvessels [26, 27], thereby impairing therapeutic efficacy.

In the present study, each patient received 2–6 cycles of HAIC, with patients in the Con group undergoing more HAIC cycles than those in the SE group ($P = 0.033 < 0.05$). Admittedly, while all enrolled patients completed more than 2 treatment cycles, ideally, we would have preferred all participants to receive at least 4 cycles of treatment—this would have enhanced the persuasiveness of our final results. Regrettably, from this perspective, the treatment completion rate was less than 40% in the SE group, compared with 75.3% in the Con group. Several factors may contribute to this discrepancy: First, it could be attributed to the better tumor control and longer survival time observed in the Con group, where patients maintained a favorable general condition and thus could tolerate more treatment cycles. Second, among patients receiving triple therapy at our center, although only a small number of patients discontinued treatment due to intolerance to treatment-related AEs, and no severe grade 5 AEs occurred in either group, this factor remains non-negligible and represents a limitation of the present study. Larger sample sizes will be required to fully validate the safety of the treatment regimens. Finally, this discrepancy may also be associated with economic factors: interventional therapy (i.e., HAIC) is considerably more costly than targeted immunotherapy. All the aforementioned factors have affected the treatment completion rate to varying degrees. To further investigate the impact of treatment cycles on clinical outcomes, patients enrolled in this study were stratified into two subgroups based on the number of treatment cycles: ≤4 cycles and >4 cycles. The differences in OS and PFS between the SE group and the Con group were compared separately within each subgroup. The results demonstrated that in the ≤4 cycles subgroup, the median OS (13.9 months vs. 9.8 months, $p = 0.023$) and median PFS (7.5 months vs. 5.9 months, $p = 0.017$) of the Con group were significantly superior to those of the SE group, with statistically significant differences ($p < 0.05$). In contrast, no statistically significant difference was observed in survival outcomes between the two groups in the >4 cycles subgroup. Specifically, the median OS of the Con group was 16.2 months vs. 13.6 months in the SE group ($p = 0.14 > 0.05$), and the median PFS of the Con group was 8.6 months versus 7.0 months in the SE group ($p = 0.08 > 0.05$). Our study data demonstrated that in the subgroup with ≤4 cycles of HAIC, patients in the Con group achieved significantly greater survival benefits. In contrast, no statistically significant difference in therapeutic efficacy was observed between the two groups when the number of HAIC cycles exceeded 4. Admittedly, the limited sample size of this study has to some extent restricted the extrapolation value of these conclusions.

However, the Con regimen demonstrated a greater frequency of AEs compared to the SE approach, with nausea and vomiting representing the predominant AEs, followed by abdominal pain, which were alleviated to varying degrees after symptomatic treatment. While grade 3–4 hepatic impairment was commonly observed with concurrent treatment, the HAIC-related liver function abnormalities were generally temporary (resolving within 3 weeks in most cases) and had negligible long-term prognostic impact. Both groups showed a high incidence of HFS, which was usually relieved after symptomatic treatment and health education. Notably, the Con group exhibited a higher rate of myelosuppression, which clinically presents as anemia(43.5%), neutropenia(60.0%), and thrombocytopenia(41.2%). These indicators typically recovered after symptomatic treatment; however, if such abnormalities are difficult to correct, it may increase the risk of infection and bleeding, and may also lead to chemotherapy termination, thereby weakening tumor control. No severe biliary sclerosis was observed in patients of either group after treatment in this study: only 24.7% (21/85) of patients in the SE group and 28.2% (24/85) in the Con group had mild elevations in ALP, GGT, TBIL, and DBIL, and most of these abnormalities resolved after treatment. No catheter or infusion pump failures were observed in this study, though this may be associated with the small sample size enrolled in the research. The incidence of postoperative infection was 10.6% (9/85) in the SE group and 14.1% (14/85) in the Con group, with all infections classified as mild. Notably, the incidence rates of hyperbilirubinemia (44.7% vs. 24.7%, $p = 0.04 < 0.05$) and anemia (43.5% vs. 16.5%, $p = 0.005 < 0.05$) in the

Con group were significantly higher than those in the SE group. Overall, no severe (grade 5) AEs occurred in either the SE or Con group, and all reported AEs were manageable and tolerable in both groups.

In general, Our results indicate that: for advanced HCC, the Con regimen offers greater advantages in terms of therapeutic efficacy compared with the SE regimen. This advantage is particularly more pronounced in the patient population that meets the following criteria: male gender, age < 60 years, having received ≥ 4 cycles of HAIC, a history of hepatitis B, serum AFP level < 400 ng/mL, achieving Child-Pugh class A for liver function, single tumor type, presence of vascular invasion, and absence of distant metastasis. Therefore, we recommend the Con regimen as the first-line treatment option for BCLC-stage HCC. The above research results indicate that under the conditions of tolerable physical status and controllable AE, timely synchronous treatment can significantly reduce intrahepatic tumor burden. Even in cases with extrahepatic metastasis, effective reduction of tumor burden can still improve the prognosis.

This study has the following limitations that should be noted: First, it adopted a retrospective study design, which carries a risk of selection bias: due to the "non-randomized" nature of retrospective data, the included samples may still fail to fully represent the target patient population. Second, this is a single-center study, with cases sourced exclusively from patients treated at our hospital between January 2020 and December 2024, resulting in a relatively small sample size. Finally, influenced by differences in patients' economic status and the treatment practices of attending physicians, there were variations in the selection of anti-angiogenic drug types and the use of PD-(L)1 inhibitors—both across different groups and among individual patients within the same group. Additionally, the number of HAIC cycles received by enrolled patients at our center was relatively low. In summary, the combined effects of the aforementioned factors have, to a certain extent, limited the reliability and generalizability of the conclusions drawn from this study. Therefore, future research should conduct large-sample, multi-center prospective cohort studies to further validate the value of the conclusions presented herein.

Conclusion

Our study indicates that for patients with BCLC stage C HCC, under the premise of manageable adverse events, the concurrent treatment regimen of HAIC combined with targeted therapy and immunotherapy may achieve control of local liver lesions. However, systemic therapy remains the standard treatment option at present. In the future, further research on combination treatment strategies is needed to provide better prognosis for patients with advanced HCC.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-026-04198-6.

Supplementary Material 1

Authors' contributions

ZL: Writing - Original Draft, Investigation. MX: Writing - Original Draft, Investigation. YX: Writing - Original Draft, Investigation. GY: Writing - Review & Editing, Conceptualization. YX: Writing - Review & Editing, Funding acquisition, Conceptualization. All authors read and approved the final manuscript.

Funding

This work was supported by the: China Postdoctoral Science Foundation (grant numbers 2023MD734156); Nanchong Science and Technology Bureau Basic Research Platform Project (grant numbers 23JCYJPT0043); Specialty Areas in Oncology, Anesthesiology and Other Fields of Sichuan Medical Association (grant numbers 2024HR03); Science and Technology Innovation Platforms and Talent Program of Sichuan Provincial Department of Science and Technology (grant numbers 2024JDKP0022); Innovation Team Program of the Affiliated Hospital of North Sichuan Medical College (grant numbers 2024CX0026); General Program of Open Research Fund of State Key Laboratory of Neuro-Oncology Drug Research and Development, (grant number SKLSIM-20251026); Joint Research Project for the Development of the Affiliated Hospital of North Sichuan Medical College and Guang'an District People's Hospital in 2025, (grant number 2025LHFZ04); Noncommunicable Chronic Diseases-National Science and Technology Major Project (grant number 2023ZD0500700).

Data availability

The data that support the findings of this study are available from Affiliated Hospital of North Sichuan Medical College, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of.Affiliated Hospital of North Sichuan Medical College.

Declarations

Ethics approval and consent to participate

Ethical approval has been obtained. All authors have approved the final version of the manuscript for submission, and the work described has not been previously published.

Consent for publication

All authors of this study agreed to publish.

Competing interests

The authors declare no competing interests.

Author details

[1]National Key Clinical Specialty - General Surgery, Hepatobiliary Surgery, Academician (Expert) Workstation, Sichuan Digestive System Disease Clinical Medical Research Center, Affiliated Hospital of North Sichuan Medical College, Nanchong 637000, P. R. China

Received: 3 September 2025 / Accepted: 8 January 2026
Published online: 27 February 2026

References

1. Sung H, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Cancer J Clin. 2021;71(3):209–49.
2. Llovet JM, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2021;7(1):6. https://doi.org/10.1038/s41572-020-00240-3.

3. He M, et al. Sorafenib plus hepatic arterial infusion of Oxaliplatin, Fluorouracil, and leucovorin vs Sorafenib alone for hepatocellular carcinoma with portal vein invasion. JAMA Oncol. 2019;5(7):953.
4. Wang Q, et al. Development of a prognostic score for recommended TACE candidates with hepatocellular carcinoma: A multicentre observational study. J Hepatol. 2019;70(5):893–903.
5. Cao Y-z, et al. Hepatic arterial infusion chemotherapy combined with systemic therapy sequentially or simultaneously for advanced hepatocellular carcinoma. Volume 74. Immunotherapy: Cancer Immunology; 2024. 1.
6. Yau T, et al. Nivolumab plus ipilimumab versus lenvatinib or Sorafenib as first-line treatment for unresectable hepatocellular carcinoma (CheckMate 9DW): an open-label, randomised, phase 3 trial. Lancet (London England). 2025;405(10492):1851–64.
7. Qin S, et al. Camrelizumab plus Rivoceranib versus Sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310): a randomised, open-label, international phase 3 study. Lancet (London England). 2023;402(10408):1133–46.
8. Jiang P, et al. Efficacy and safety of HAIC-FOLFOX plus tyrosine kinase inhibitors and immune checkpoint inhibitors as First-line treatment for unresectable advanced hepatocellular carcinoma: A systematic review and Meta-Analysis. Acad Radiol. 2025;32(8):4595–606.
9. Lyu N, et al. Hepatic arterial infusion of oxaliplatin plus fluorouracil/leucovorin vs. sorafenib for advanced hepatocellular carcinoma. J Hepatol. 2018;69(1):60–9.
10. Lin W, et al. Oncological and reproductive outcomes after fertility-sparing surgery for stage I mucinous ovarian carcinoma. Front Oncol. 2022. https://doi.org/10.3389/fonc.2022.856818.
11. Zhang J, et al. Surgical conversion for initially unresectable locally advanced hepatocellular carcinoma using a triple combination of angiogenesis inhibitors, anti-PD-1 antibodies, and hepatic arterial infusion chemotherapy: a retrospective study. Front Oncol. 2021. https://doi.org/10.3389/fonc.2021.729764.
12. Lai Z, et al. Lenvatinib, Toripalimab plus hepatic arterial infusion chemotherapy in patients with high-risk advanced hepatocellular carcinoma: A biomolecular exploratory, phase II trial. Eur J Cancer. 2022;174:68–77.
13. Bedognetti D, et al. Concurrent vs sequential adjuvant chemotherapy and hormone therapy in breast cancer: A multicenter randomized phase III trial. JNCI: J Natl Cancer Inst. 2011;103(20):1529–39.
14. Sun L, et al. Sequential vs. concurrent systemic therapies in combination with FOLFOX-HAIC for locally advanced hepatocellular carcinoma: a single-center, real-world cohort study. BMC Cancer. 2024;24(1):1168.
15. Vogel A, et al. Updated treatment recommendations for hepatocellular carcinoma (HCC) from the ESMO clinical practice guidelines. Ann Oncol. 2021;32(6):801–5.
16. Eisenhauer EA, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47.
17. Haupt S, et al. Sex disparities matter in cancer development and therapy. Nat Rev Cancer. 2021;21(6):393–407.
18. Zhang T-Q, et al. Camrelizumab (a PD-1 inhibitor) plus apatinib (an VEGFR-2 inhibitor) and hepatic artery infusion chemotherapy for hepatocellular carcinoma in Barcelona Clinic Liver Cancer stage C (TRIPLET): a phase II study. Signal Transduct Target Ther. 2023. https://doi.org/10.1038/s41392-023-01663-6.
19. Wang Y, et al. Anti-PD-1/L1 lead-in before MAPK inhibitor combination maximizes antitumor immunity and efficacy. Cancer Cell. 2021;39(10):1375–e13876.
20. Yu B, et al. Tyrosine kinase inhibitors plus Anti-PD-1 antibodies with hepatic arterial infusion chemotherapy or transarterial chemoembolization for unresectable hepatocellular carcinoma. J Hepatocellular Carcinoma. 2023;10:1735–48.
21. Liu J, Zhang S, Shao H. Hepatic arterial infusion chemotherapy plus lenvatinib and PD-1 inhibitors versus lenvatinib plus PD-1 inhibitors as first-line treatment for hepatocellular carcinoma with high tumour burden and portal vein tumour thrombus (CHANCE 2416): study protocol of a multicentre, retrospective, target trial emulation design. BMJ Open. 2025;15(9):e099510.
22. Jiang P, et al. Hepatic artery infusion chemotherapy combined with lenvatinib and PD-1 inhibitors in the treatment of intermediate and advanced unresectable hepatocellular carcinoma. Oncol Lett. 2025;30(3):437.
23. Cheng A-L, et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol. 2021;76(4):862–73.
24. Srivastava S, et al. Immunogenic chemotherapy enhances recruitment of CAR-T cells to lung tumors and improves antitumor efficacy when combined with checkpoint Blockade. Cancer Cell. 2021;39(2):193–e20810.
25. Lee WS, et al. Combination of anti-angiogenic therapy and immune checkpoint Blockade normalizes vascular-immune crosstalk to potentiate cancer immunity. Exp Mol Med. 2020;52(9):1475–85.
26. de Ruiz M, et al. β-Catenin activation promotes immune escape and resistance to Anti–PD-1 therapy in hepatocellular carcinoma. Cancer Discov. 2019;9(8):1124–41.
27. Huang X-Y, et al. Circular RNA circMET drives immunosuppression and anti-PD1 therapy resistance in hepatocellular carcinoma via the miR-30-5p/snail/DPP4 axis. Mol Cancer. 2020. https://doi.org/10.1186/s12943-020-01213-6.

Publisher's Note