Original Article

Efficacy and safety of arterial FOLFOX chemotherapy plus anti-PD-(L)1 immunotherapy as a first-line treatment for unresectable intrahepatic cholangiocarcinoma: a propensity score matching analysis

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Background: Given the limited efficacy of current first-line therapies, there is an urgent need to develop novel treatment strategies to improve the prognosis of patients with unresectable intrahepatic cholangiocarcinoma (uICC). This study aimed to evaluate the efficacy and safety of hepatic arterial infusion chemotherapy (HAIC) with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) regimens (HAIC-FO) plus anti-programmed death-(ligand) 1 immunotherapy [αPD-(L)1] antibody [HAIC+αPD-(L)1] compared to systemic chemotherapy (SYS) plus αPD-(L)1 antibody [SYS+αPD-(L)1] as a first-line treatment for patients with uICC.

Methods: In this retrospective study, treatment-naive uICC patients who were treated with HAIC+αPD-(L)1 or SYS+αPD-(L)1 were included. The clinical characteristics, therapeutic outcomes, and adverse events (AEs) of the patients in the two groups were compared. Propensity score matching (PSM) was performed to minimize biases between groups.

Results: From January 2019 to January 2023, a total of 182 patients were enrolled; 147 patients were included in the HAIC+αPD-(L)1 group and 35 patients were included in the SYS+αPD-(L)1 group. After PSM, 61 and 26 patients were included in the HAIC+αPD-(L)1 and SYS+αPD-(L)1 groups, respectively. The HAIC+αPD-(L)1 group had longer median overall survival (mOS), median progression-free survival (mPFS), and median intrahepatic PFS (mIPFS) than did the SYS+αPD-(L)1 group (mOS: 14.5 *vs.* 10.5 months, P=0.02; mPFS: 10.4 *vs.* 6.4 months, P=0.02; mIPFS: 11.4 *vs.* 6.5 months, P<0.001). The overall incidence of AEs was comparable between the two groups, but the HAIC+αPD-(L)1 group had a lower incidence of grade 3–4 AEs related to anemia, leukopenia, weight loss, and fatigue.

Conclusions: HAIC+αPD-(L)1 had acceptable toxic effects and might improve outcomes compared to SYS+αPD-(L)1 as a first-line treatment for patients with uICC.

Keywords: Unresectable intrahepatic cholangiocarcinoma (uICC); hepatic arterial infusion chemotherapy (HAIC); systemic chemotherapy (SYS); anti-programmed death-(ligand) 1 immunotherapy [αPD-(L)1]; propensity score matching (PSM)

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Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer worldwide after hepatocellular carcinoma (HCC) (1,2). Complete surgical resection is currently recommended as the first-line and curative approach for treating ICC; however, 70–80% of patients are initially diagnosed with local unresectability or distant metastasis, missing the opportunity for surgical treatment (3). Systemic chemotherapy (SYS), such as gemcitabine plus cisplatin (GEMCIS) or gemcitabine plus oxaliplatin (GEMOX), is recommended as the first-line treatment for patients with unresectable ICC (uICC) (4). Nevertheless, the majority of these patients have a poor prognosis, with a median survival of only approximately 1 year.

In recent years, combination therapy based on immune checkpoint inhibitors (ICIs), such as anti-programmed death-(ligand) 1 [PD-(L)1] antibodies, has emerged as a prominent trend in the field of cancer treatment. Clinical trials like TOPAZ-1 and KEYNOTE-966 have demonstrated significant survival benefits for patients with advanced biliary tract cancer, including uICC, when treated with SYS plus anti-PD-(L)1 antibodies compared to SYS alone (5,6). Consequently, the combination of GEMCIS with durvalumab (an anti-PD-L1 antibody) or pembrolizumab (an anti-PD-1 antibody) has been approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA), establishing it as the current recommended first-line treatment approach in international guidelines (2-4,7).

Importantly, SYS, although effective at attacking cancer cells systemically, can result in significant damage to normal tissues, leading to toxic side effects. This not only may force patients to discontinue treatment prematurely, but also raises concerns regarding potential antagonistic interactions between SYS and immunotherapy due to chemotherapy-induced immune system impairment (8,9). In theory, optimizing chemotherapy further is a promising strategy to enhance the antitumor efficacy of anti-PD-(L)1 antibodies.

Hepatic arterial infusion chemotherapy (HAIC) is a regional chemotherapy technique that delivers high-concentration chemotherapeutic agents directly to tumor sites through the hepatic artery (10). HAIC with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) regimens (HAIC-FO) shows tolerable toxicity and promising efficacy in patients with colorectal liver metastases, unresectable perihilar cholangiocarcinoma, and advanced HCC (11-14). The previous studies have demonstrated the favorable antitumor activity of HAIC either as a monotherapy or in combination with SYS in uICC patients (15,16). In 2016, Konstantinidis *et al.* reported that in patients with liver-confined uICC, the median overall survival (mOS) was longer in those who received HAIC plus SYS than in those who received SYS alone (30.8 *vs.* 18.4 months, P<0.001) (17). A phase II

Highlight box

Key findings

- Hepatic arterial infusion chemotherapy with infusional fluorouracil, leucovorin, and oxaliplatin regimens (HAIC-FO) combined with anti-programmed death-(ligand) 1 immunotherapy [αPD-(L)1] may offer superior efficacy compared to systemic chemotherapy (SYS) combined with αPD-(L)1 as a first-line treatment for unresectable intrahepatic cholangiocarcinoma (uICC) patients, while maintaining an acceptable safety profile.

What is known and what is new?

- The combination of SYS and αPD-(L)1 has emerged as the primary first-line treatment regimen for uICC patients. However, due to the potential negative impact of SYS on the immune system, there may exist an antagonistic interaction between SYS and immunotherapy.
- The combination of HAIC-FO and αPD-(L)1 showed superior median overall survival, median progression-free survival (PFS), median intrahepatic PFS, and objective response rate as a first-line treatment option for patients with uICC compared to the combination of SYS and αPD-(L)1, while maintaining manageable adverse effects.

What is the implication, and what should change now?

- As a first-line therapeutic approach for patients with uICC, the combination of HAIC-FO and αPD-(L)1 may exhibit superior treatment efficacy compared to the combination of SYS and αPD-(L)1, while maintaining manageable adverse effects.
- The combination therapy of HAIC-FO and anti-PD-(L)1 may present a potential first-line treatment option for patients with uICC. However, further investigation through prospective randomized controlled trials is necessary to fully elucidate the potential role of this combined therapy in uICC patients.

single-arm study revealed that the median progression-free survival (mPFS) was 11.8 months, the mOS was 25 months, and the objective response rate (ORR) reached 58%, indicating a high level of antitumor activity, in patients with liver-confined uICC treated with HAIC combined with GEMOX (18). Recently, Li *et al.* conducted a retrospective analysis of uICC patients with extrahepatic oligometastasis and reported that the mOS and intrahepatic PFS (IPFS) were significantly longer, and mortality due to liver failure was significantly reduced (42% *vs.* 72%, P=0.002) in the group treated with HAIC plus SYS than in the group treated with SYS alone (OS: 15.8 *vs.* 12.7 months, P=0.023; IPFS: 9.7 *vs.* 6.1 months, P<0.001) (19). These results suggest that adding systemic therapy to HAIC may be a beneficial clinical approach.

Compared to SYS, localized drug delivery through HAIC may increase tumor cell death and exposure to tumor antigens while minimizing the impact of chemotherapy on the immune system (15,16,20). This localized approach could induce a strong antitumor immune response (8). Preclinical studies have shown that compared with SYS, localized chemotherapy may enhance antitumor immune responses and improve the efficacy of anti-PD-(L)1 therapy (8,21,22). Therefore, we hypothesize that combining HAIC-FO with anti-PD-(L)1 immunotherapy [αPD-(L)1] may improve survival outcomes in uICC patients.

To date, there have been limited reports investigating the efficacy of HAIC-FO combined with αPD-(L)1 in uICC patients. In this study, we conducted a comparative analysis to evaluate the effectiveness and safety of HAIC-FO plus anti-PD-(L)1 antibody *vs.* SYS plus anti-PD-(L)1 antibody in uICC patients. The findings from this study may offer novel insights into the first-line treatment approach for uICC. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-552/rc).

Methods

Study design and population

This study was approved by the Ethics Committee of Sun Yat-sen University Cancer Center (No. G2024-080-01). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived. Between January 2019 and January 2023, baseline and follow-up data were collected for 182 patients with uICC [99 men (mean age, 57 years; range, 55–59 years) and 83 women (mean age, 55 years; range, 52–57 years)]. Among these patients, 147 received HAIC-FO plus anti-PD-(L)1 immunotherapy antibody [hereafter referred to as the HAIC+αPD-(L)1 group], while 35 received SYS plus anti-PD-(L)1 immunotherapy antibody [hereafter referred to as the SYS+αPD-(L)1 group]. The last follow-up date on which clinical data were collected was July 2023.

Patients who met the following criteria were included in this study: aged 18 years or older; had histopathologically confirmed unresectable or metastatic ICC according to the World Health Organization (WHO) classification (23); had received at least one cycle of HAIC-FO or SYS treatment; and had adequate blood/bone marrow (leukocyte count >3.0×10^9/L, hemoglobin level >8.0 g/L, and platelet count >60×10^9/L), liver [alanine transaminase (ALT) and aspartate aminotransferase (AST) levels <5 times the upper limit of normal, albumin (ALB) level >2.8 g/L, total bilirubin level <2.8 g/L], renal (serum creatinine level <1.5 times the upper limit of normal) and coagulation (prothrombin time <6 seconds) function. The exclusion criteria included any history of antitumor therapy, a Child-Pugh score of C, an Eastern Cooperative Oncology Group (ECOG) performance score >2, the absence of enhanced computed tomography (CT) or magnetic resonance imaging (MRI) examination before treatment, and loss to follow-up.

Treatment management

The HAIC-FO treatment approach has been described in detail in previous studies (13,14). In brief, all patients in the HAIC+αPD-(L)1 group underwent arterial catheter placement under the guidance of digital subtraction angiography. Subsequently, they received continuous infusion through the catheter according to the FOLFOX regimen (oxaliplatin 130 mg/m^2, leucovorin 200 mg/m^2, bolus fluorouracil 400 mg/m^2, and infusional fluorouracil 2,400 mg/m^2) in each 3-week cycle. During treatment, patients with no disease progression received a maximum of 8 cycles of HAIC-FO therapy.

Concurrently, all patients in the SYS+αPD-(L)1 group were treated following the first-line chemotherapy recommendations of the National Comprehensive Cancer Network (NCCN) guidelines (24). Table S1 shows the type of chemotherapy used in the SYS+αPD-(L)1 treatment group for patients. PD-(L)1 inhibitors were administered intravenously every 3 weeks. These inhibitors included durvalumab, pembrolizumab, nivolumab, toripalimab,

tislelizumab, and sintilimab.

Assessment and end points

All patients underwent regular follow-ups within 1 week prior to the initiation of treatment, followed by subsequent routine follow-ups every 3±1 week and at the end of the treatment. OS was defined as the duration from the commencement of the treatment to the date of death from any cause or the last patient follow-up (July 2023). PFS referred to the interval from the start of the treatment to the time of disease progression, death, or the last follow-up. IPFS was defined as the time interval from the start of treatment to the occurrence of intrahepatic tumor progression (including primary tumor progression and emergence of new intrahepatic lesions), death, or the last follow-up date, regardless of extrahepatic metastasis. Tumor evaluations were performed using dynamic contrast-enhanced MRI or CT, in line with the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) (25). The ORR encompassed the percentage of patients with either a complete response (CR) or partial response (PR). The disease control rate (DCR) included the sum of the ORR and the percentage of patients with stable disease (SD). Treatment-associated adverse events (AEs) were evaluated based on version 5.0 of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE).

Statistical analysis

Baseline and matched characteristics were compared using standard tests for continuous variables (Mann-Whitney *U* test and Wilcoxon signed-rank test) and categorical variables (χ^2 test or Fisher's exact test). To minimize potential confounding effects, we employed propensity score matching (PSM). This method was designed to balance covariates between the HAIC+αPD-(L)1 and SYS+αPD-(L)1 groups, ensuring that the observed outcome differences primarily arose from the treatment itself rather than other confounding variables. This model included sex, age, hepatitis B virus (HBV) status, Child-Pugh stage, tumor size, tumor number, tumor distribution, macrovascular invasion status, regional lymph node metastasis status, distant lymph node metastasis status, number of extrahepatic metastatic sites, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels, and tumor differentiation status. Using the patient demographics and clinical features described above, binary logistic regression was performed to compute the propensity scores, followed by 4:1 greedy nearest-neighbor matching with a caliper of 0.2, based on the MatchIt package in R.

Survival curves were plotted using the Kaplan-Meier method, with differences in prognostic variables compared using the log-rank test. Multivariate Cox regression analysis was performed to determine the independent factors significantly associated with survival, while adjusting for potential confounders. A backward stepwise regression method was employed to select the best combination of variables from the univariate analysis for inclusion in the multivariate analysis model. All the statistical analyses were conducted using R software (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria) or SPSS (version 25.0; IBM, Armonk, NY, USA). All P values were two-sided, with P values less than 0.05 considered to indicate statistical significance.

Results

Patient characteristics

From January 2019 to January 2023, a total of 946 patients were pathologically diagnosed with ICC at the Sun Yat-sen Cancer Center. After comprehensive assessment, 182 patients with uICC met the inclusion criteria of this study. The detailed patient selection procedure is shown in *Figure 1*.

The baseline demographic and clinical characteristics of the two groups are presented in *Table 1*. There were significant differences in baseline features between the groups in terms of tumor distribution (P=0.01), regional lymph node metastasis (P=0.003), distant lymph node metastasis (P<0.001), and the number of extrahepatic metastatic sites (P<0.001). After performing PSM for all patients in the HAIC+αPD-(L)1 and SYS+αPD-(L)1 groups, there were 61 and 26 remaining patients in the two groups respectively, with well-balanced baseline characteristics. The types of second-line treatments before and after PSM are summarized in *Table 2*, and Table S2 shows the baseline metastasis status of the patients.

Survival analyses

Before PSM, the HAIC+αPD-(L)1 group exhibited a significantly longer median OS and PFS than did the SYS+αPD-(L)1 group (mOS: 16.6 *vs.* 12.2 months, P<0.001; mPFS: 9.6 *vs.* 6.9 months, P=0.008; *Figure 2A*,*2B*). The

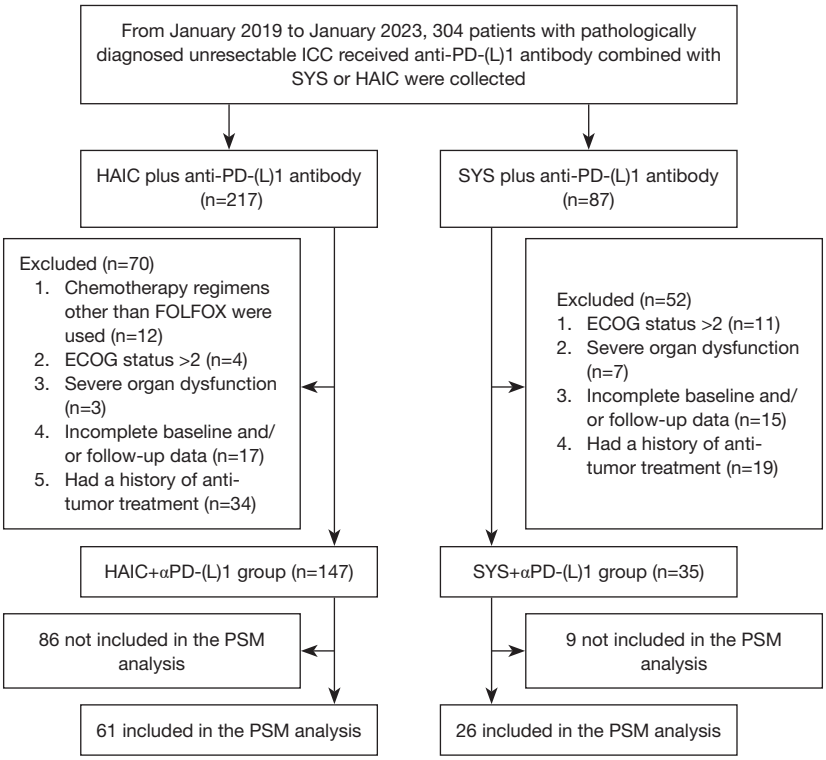

Figure 1 A flowchart shows the patient selection of this study. ICC, intrahepatic cholangiocarcinoma; PD-(L)1, programmed death-(ligand) 1; SYS, systemic chemotherapy; HAIC, hepatic arterial infusion chemotherapy; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; ECOG, Eastern Cooperative Oncology Group; αPD-(L)1, anti-programmed death-(ligand) 1 immunotherapy; PSM, propensity score matching.

Table 1 Patient demographics and baseline characteristics before and after PSM

Characteristics	Unmatched			Matched		
	HAIC+αPD-(L)1 (n=147)	SYS+αPD-(L)1 (n=35)	P value	HAIC+αPD-(L)1 (n=61)	SYS+αPD-(L)1 (n=26)	P value
Sex			0.70			0.58
Male	81 (55.10)	18 (51.43)		31 (50.82)	15 (57.69)	
Female	66 (44.90)	17 (48.57)		30 (49.18)	11 (42.31)	
Age (years)			0.79			0.80
≤60	96 (65.31)	22 (62.86)		37 (60.66)	15 (57.69)	
>60	51 (34.69)	13 (37.14)		24 (39.34)	11 (42.31)	
HBV			0.56			0.64
Absent	104 (70.75)	23 (65.71)		43 (70.49)	17 (65.38)	
Present	43 (29.25)	12 (34.29)		18 (29.51)	9 (34.62)	
Child-Pugh stage			0.10			0.76
A	130 (88.44)	27 (77.14)		51 (83.61)	21 (80.77)	
B	17 (11.56)	8 (22.86)		10 (16.39)	5 (19.23)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Unmatched			Matched		
	HAIC+αPD-(L)1 (n=147)	SYS+αPD-(L)1 (n=35)	P value	HAIC+αPD-(L)1 (n=61)	SYS+αPD-(L)1 (n=26)	P value
Tumor size (mm)			0.34			0.87
≤80	75 (51.02)	21 (60.00)		34 (55.74)	15 (57.69)	
>80	72 (48.98)	14 (40.00)		27 (44.26)	11 (42.31)	
Tumor number			0.33			0.87
≤3	55 (37.41)	10 (28.57)		20 (32.79)	9 (34.62)	
>3	92 (62.59)	25 (71.43)		41 (67.21)	17 (65.38)	
Tumor distribution			0.01*			0.44
Unilobar	80 (54.42)	11 (31.43)		29 (47.54)	10 (38.46)	
Bilobar	67 (45.58)	24 (68.57)		32 (52.46)	16 (61.54)	
Macrovascular invasion			0.96			0.72
Absent	93 (63.27)	22 (62.86)		40 (65.57)	16 (61.54)	
Present	54 (36.73)	13 (37.14)		21 (34.43)	10 (38.46)	
Regional lymph node metastasis			0.003*			0.26
Absent	65 (44.22)	6 (17.14)		19 (31.15)	5 (19.23)	
Present	82 (55.78)	29 (82.86)		42 (68.85)	21 (80.77)	
Distant lymph node metastasis			<0.001*			0.44
Absent	124 (84.35)	19 (54.29)		47 (77.05)	18 (69.23)	
Present	23 (15.65)	16 (45.71)		14 (22.95)	8 (30.77)	
Number of extrahepatic metastatic sites			<0.001*			0.61
0	110 (74.83)	16 (45.71)		38 (62.30)	15 (57.69)	
1	31 (21.09)	10 (28.57)		18 (29.51)	7 (26.92)	
2	6 (4.08)	9 (25.71)		5 (8.20)	4 (15.38)	
CEA (ng/mL)			0.49			0.73
≤5	85 (57.82)	18 (51.43)		33 (54.10)	13 (50.00)	
>5	62 (42.18)	17 (48.57)		28 (45.90)	13 (50.00)	
CA19-9 (U/mL)			0.11			0.62
≤100	62 (42.18)	20 (57.14)		27 (44.26)	13 (50.00)	
>100	85 (57.82)	15 (42.86)		34 (55.74)	13 (50.00)	
Tumor differentiation			>0.99			0.92
Well	4 (2.72)	1 (2.86)		2 (3.28)	1 (3.85)	
Moderately	80 (54.42)	19 (54.29)		30 (49.18)	15 (57.69)	
Poorly	48 (32.65)	12 (34.29)		23 (37.70)	8 (30.77)	
Not specified	15 (10.20)	3 (8.57)		6 (9.84)	2 (7.69)	

*, P<0.05. PSM, propensity score matching; HAIC+αPD-(L)1, HAIC-FO plus αPD-(L)1 antibody; HAIC-FO, HAIC with infusional FOLFOX regimens; HAIC, hepatic arterial infusion chemotherapy; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; αPD-(L)1, anti-programmed death-(ligand) 1 immunotherapy; SYS+αPD-(L)1, SYS plus αPD-(L)1 antibody; SYS, systemic chemotherapy; HBV, hepatitis B virus; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

Table 2 Subsequent treatment options after disease progression

Variables	HAIC+αPD-(L)1 (n=61)	SYS+αPD-(L)1 (n=26)
Chemotherapy	10 (16.4)	7 (26.9)
Radiotherapy	1 (1.6)	2 (7.7)
TACE	1 (1.6)	0 (0.0)
Percutaneous thermal ablation	1 (1.6)	0 (0.0)
TKI	9 (14.8)	2 (7.7)
ICI	4 (6.6)	1 (3.8)
TKI + ICI	12 (19.7)	4 (15.4)
Chemotherapy + TKI	0 (0.0)	1 (3.8)
Chemotherapy + ICI	0 (0.0)	1 (3.8)
Chemotherapy + TKI + ICI	2 (3.3)	2 (7.7)
Best supportive care	21 (34.4)	6 (23.1)

Data are presented as n (%). HAIC+αPD-(L)1, HAIC-FO plus αPD-(L)1 antibody; HAIC-FO, HAIC with infusional FOLFOX regimens; HAIC, hepatic arterial infusion chemotherapy; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; αPD-(L)1, anti-programmed death-(ligand) 1 immunotherapy; SYS+αPD-(L)1, SYS plus αPD-(L)1 antibody; SYS, systemic chemotherapy; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor.

estimated OS rates for HAIC+αPD-(L)1 and SYS+αPD-(L)1 groups were 70.3% [95% confidence interval (CI): 63.2% to 78.1%] and 51.7% (95% CI: 37.1% to 71.9%) at 1 year, and 33.8% (95% CI: 26.3% to 43.5%) and 13.7% (95% CI: 5.19% to 36.0%) at 2 years, respectively. In the matched cohort, a significant difference in the mOS and mPFS persisted between the two groups (mOS: 14.5 *vs.* 10.5 months, P=0.02; mPFS: 10.4 *vs.* 6.4 months, P=0.02; *Figure 2C,2D*). The estimated OS rates for HAIC+αPD-(L)1 and SYS+αPD-(L)1 groups were 69.8% (95% CI: 59.0%, 82.5%) and 40.0% (95% CI: 24.7%, 64.6%) at 1 year, and 27.3% (95% CI: 6.76%, 43.5%) and 17.1% (95% CI: 6.76%, 43.5%) at 2 years, respectively (Table S3).

As shown in *Figure 3*, the median IPFS (mIPFS) in the HAIC+αPD-(L)1 group was significantly longer than that in the SYS+αPD-(L)1 group regardless of whether a PSM was performed (before PSM: 11.4 *vs.* 6.9 months, P<0.001; after PSM: 11.4 *vs.* 6.5 months, P<0.001).

The subgroup analyses related to OS and PFS after PSM are shown in *Figure 4* and Figure S1, respectively. HAIC+αPD-(L)1 therapy showed a clinical benefit for OS in male patients [hazard ratio (HR) =0.22; 95% CI: 0.09–0.50; P<0.001], and patients with a tumor diameter >80 mm (HR =0.41; 95% CI: 0.18–0.91; P=0.03), macrovascular invasion (HR =0.32; 95% CI: 0.13–0.83; P=0.02) and a CEA level >5 ng/mL (HR =0.36; 95% CI: 0.17–0.74; P=0.006) benefited from HAIC+αPD-(L)1 therapy. Subgroup analysis of PFS revealed that male patients (HR =0.31; 95% CI: 0.15–0.65; P=0.002), patients with a tumor diameter >80 mm (HR =0.43; 95% CI: 0.20–0.93; P=0.03), with macrovascular invasion (HR =0.40; 95% CI: 0.17–0.93; P=0.03), with a CEA level >5 ng/mL (HR =0.38; 95% CI: 0.18–0.80; P=0.01) and with a CA19-9 level >100 U/mL (HR =0.26; 95% CI: 0.12–0.56; P<0.001) benefited from HAIC+αPD-(L)1 therapy.

Prognostic factors for OS and PFS in the HAIC+αPD-(L)1 group

As shown in *Table 3*, we performed univariate and multivariate analyses of factors affecting OS and PFS in the HAIC+αPD-(L)1 group. After adjusting for potential confounding factors, Child-Pugh class B (HR =2.22; 95% CI: 1.20–4.11; P=0.01), tumor distribution across liver lobes (HR =2.28; 95% CI: 1.48–3.53; P<0.001), distant lymph node metastasis (HR =1.92; 95% CI: 1.02–3.62; P=0.04), extrahepatic metastasis (HR =1.67; 95% CI: 1.03–2.70; P=0.04), and a CA19-9 level >100 U/mL (HR =2.24; 95% CI: 1.42–3.54; P<0.001) were found to be independent risk factors associated with OS, while Child-Pugh class B (HR =2.04; 95% CI: 1.13–3.70; P=0.02), the presence of >3 intrahepatic tumors (HR =2.07; 95% CI: 1.38–3.11; P<0.001) and a CA19-9 level >100 U/mL (HR =1.79; 95% CI: 1.16–2.75; P=0.008) were identified as independent risk factors associated with PFS.

Radiological response rate

The patients' tumor response evaluation results are detailed in *Table 4*. The ORR of the HAIC+αPD-(L)1 group was greater than that of the SYS+αPD-(L)1 group before (53.7% *vs.* 28.6%, P=0.007) and after (50.8% *vs.* 26.9%, P=0.04) PSM, but there was no significant difference in the DCR between the two groups (before PSM: 91.8% *vs.* 82.9%, P=0.11; after PSM: 91.8% *vs.* 84.6%, P=0.31).

As shown in *Figure 5*, the mOS and mPFS of CR + PR, SD, and PD patients in the HAIC+αPD-(L)1 group were analyzed. The results show that the mOS and mPFS of CR + PR patients are significantly longer than those of SD (mOS:

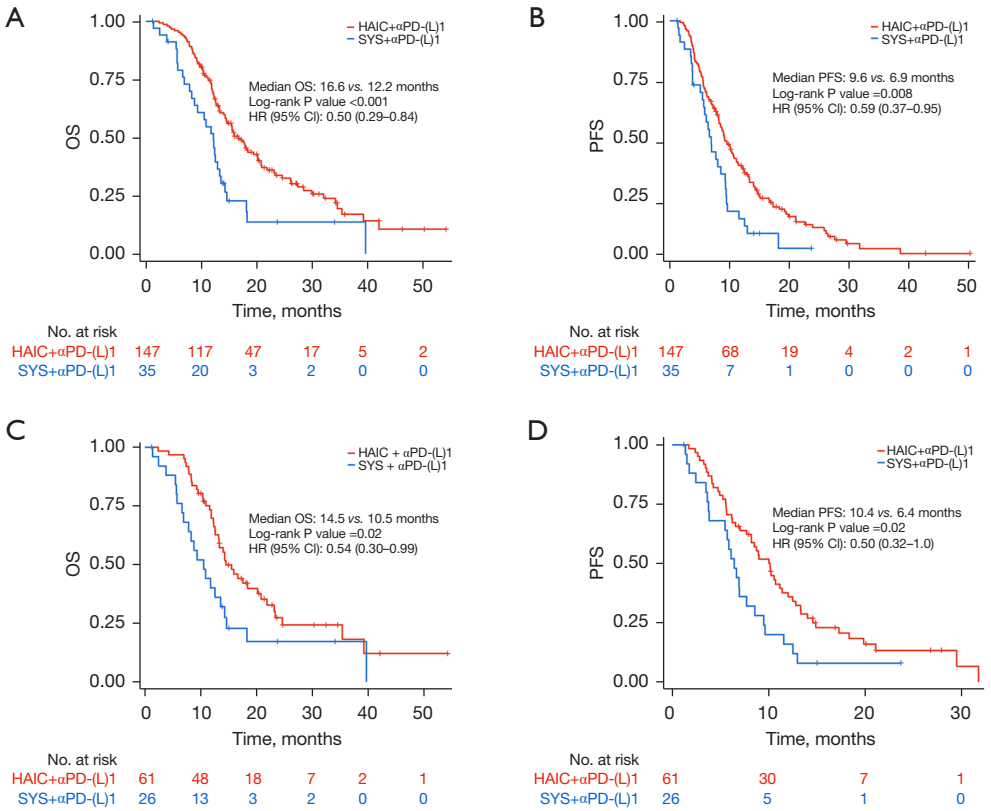

Figure 2 Kaplan-Meier estimates of OS and PFS before (A,B) and after (C,D) PSM in uICC patients treated with HAIC+αPD-(L)1 or SYS+αPD-(L)1 as first-line treatments. OS, overall survival; HAIC+αPD-(L)1, HAIC-FO plus αPD-(L)1 antibody; HAIC-FO, HAIC with infusional FOLFOX regimens; HAIC, hepatic arterial infusion chemotherapy; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; αPD-(L)1, anti-programmed death-(ligand) 1 immunotherapy; SYS+αPD-(L)1, SYS plus αPD-(L)1 antibody; SYS, systemic chemotherapy; HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; PSM, propensity score matching; uICC, unresectable intrahepatic cholangiocarcinoma.

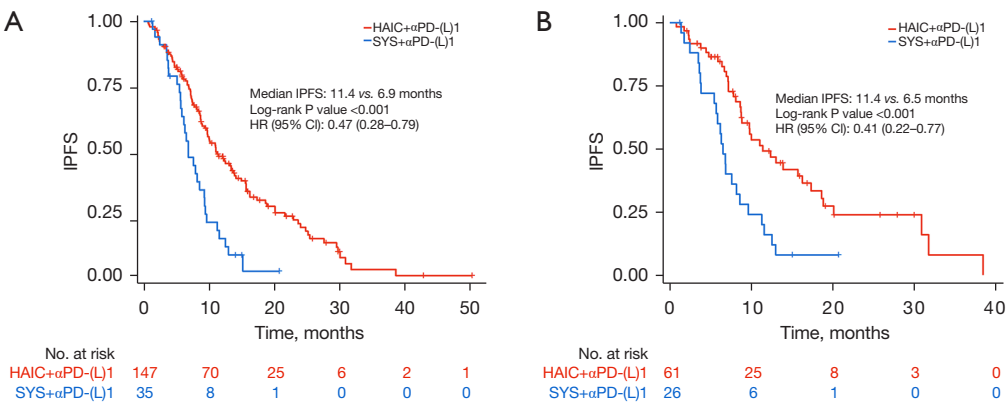

Figure 3 Kaplan-Meier estimates of IPFS before (A) and after (B) PSM in uICC patients treated with HAIC+αPD-(L)1 or SYS+αPD-(L)1 as first-line treatments. IPFS, intrahepatic progression-free survival; HAIC+αPD-(L)1, HAIC-FO plus αPD-(L)1 antibody; HAIC-FO, HAIC with infusional FOLFOX regimens; HAIC, hepatic arterial infusion chemotherapy; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; αPD-(L)1, anti-programmed death-(ligand) 1 immunotherapy; SYS+αPD-(L)1, SYS plus αPD-(L)1 antibody; SYS, systemic chemotherapy; HR, hazard ratio; CI, confidence interval; PSM, propensity score matching; uICC, unresectable intrahepatic cholangiocarcinoma.

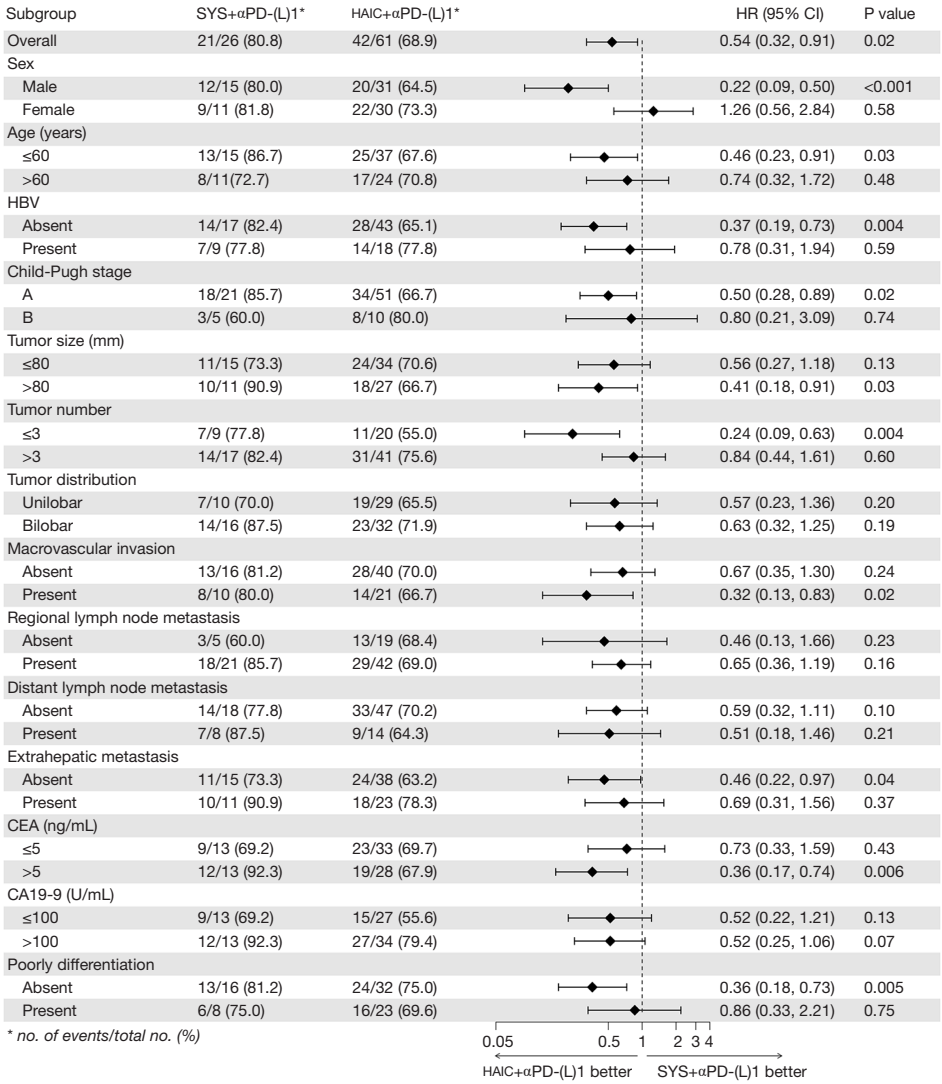

Figure 4 Forest plot analysis of factors associated with OS. SYS+αPD-(L)1, SYS plus αPD-(L)1 antibody; SYS, systemic chemotherapy; αPD-(L)1, anti-programmed death-(ligand) 1 immunotherapy; HAIC+αPD-(L)1, HAIC-FO plus αPD-(L)1 antibody; HAIC-FO, HAIC with infusional FOLFOX regimens; HAIC, hepatic arterial infusion chemotherapy; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; OS, overall survival.

18.6 *vs.* 11.2 months, P=0.005; mPFS: 13.0 *vs.* 6.9 months, P=0.004) and PD patients (mOS: 18.6 *vs.* 4.1 months, P<0.001; mPFS: 13.0 *vs.* 1.8 months, P<0.001).

As shown in Table S4, the progression of the disease is presented during the follow-up period. The results showed that the HAIC+αPD-(L)1 group mainly consisted of extrahepatic metastasis, which was significantly higher than the SYS+αPD-(L)1 group (34.0% *vs.* 11.4%, P=0.009) before PSM but no significant statistical difference after PSM (29.5% *vs.* 11.5%, P=0.07). On the contrary, the proportion of disease progression due to primary tumor was significantly lower in the HAIC+αPD-(L)1 group than in the SYS+αPD-(L)1 group before PSM (6.1% *vs.* 22.9%, P=0.002), and after PSM (4.9% *vs.* 26.9%, P=0.003).

Twenty-two out of 147 patients (15.0%) underwent radical surgery after receiving HAIC-FO combined with αPD-(L)1, including 3 (2.0%) undergoing ablation and 19 (13.0%) undergoing resection. Additionally, 19 out of 98 (19.4%) patients with locally advanced disease successfully underwent radical surgery, including 2 (2.0%) undergoing

Table 3 Univariate and multivariate analyses of prognostic factors for OS and PFS in the HAIC+αPD-(L)1 group

Characteristics	OS				PFS			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Sex (men/women)	1.31 (0.88, 1.96)	0.19			1.34 (0.94, 1.93)	0.11		
Age (>60/≤60 years)	1.18 (0.79, 1.78)	0.42			0.82 (0.56, 1.21)	0.32		
HBV (yes/no)	1.08 (0.71, 1.66)	0.71	1.41 (0.89, 2.21)	0.14	1.05 (0.71, 1.54)	0.81		
Child-Pugh stage (B/A)	2.31 (1.33, 4.02)	0.003	2.22 (1.20, 4.11)	0.01*	2.16 (1.27, 3.68)	0.004	2.04 (1.13, 3.70)	0.02*
Tumor size (>80/≤80 mm)	1.31 (0.88, 1.94)	0.19			1.4 (0.98, 2.00)	0.06		
Tumor number (>3/≤3)	1.97 (1.28, 3.04)	0.002			2.01 (1.37, 2.95)	<0.001	2.07 (1.38, 3.11)	<0.001*
Tumor distribution (unilobar/bilobar)	2.35 (1.55, 3.54)	<0.001	2.28 (1.48, 3.53)	<0.001*	1.56 (1.08, 2.24)	0.02		
Macrovascular invasion (yes/no)	0.99 (0.66, 1.49)	0.97			1.03 (0.71, 1.49)	0.88		
Regional lymph node metastasis (yes/no)	1.52 (1.02, 2.28)	0.04			1.41 (0.98, 2.02)	0.07		
Distant lymph node metastasis (yes/no)	1.78 (0.99, 3.18)	0.052	1.92 (1.02, 3.62)	0.04*	1.44 (0.87, 2.40)	0.16		
Extrahepatic metastasis (yes/no)	2.11 (1.37, 3.27)	<0.001	1.67 (1.03, 2.70)	0.04*	1.81 (1.21, 2.70)	0.004		
CEA (>5/≤5 ng/mL)	1.79 (1.20, 2.66)	0.004			1.69 (1.18, 2.42)	0.005	1.38 (0.91, 2.09)	0.13
CA19-9 (>100/≤100 U/mL)	2.04 (1.34, 3.10)	<0.001	2.24 (1.42, 3.54)	<0.001*	1.79 (1.24, 2.60)	0.002	1.79 (1.16, 2.75)	0.008*
Poorly differentiation (yes/no)	1.23 (0.81, 1.87)	0.34	1.45 (0.93, 2.26)	0.10	1.24 (0.84, 1.82)	0.28	1.41 (0.95, 2.10)	0.09

*, P<0.05. OS, overall survival; PFS, progression-free survival; HAIC+αPD-(L)1, HAIC-FO plus αPD-(L)1 antibody; HAIC-FO, HAIC with infusional FOLFOX regimens; HAIC, hepatic arterial infusion chemotherapy; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; αPD-(L)1, anti-programmed death-(ligand) 1 immunotherapy; HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

Table 4 Summary of response rates before and after PSM

Best response	Before PSM			After PSM		
	HAIC+αPD-(L)1 (n=147)	SYS+αPD-(L)1 (n=35)	P value	HAIC+αPD-(L)1 (n=61)	SYS+αPD-(L)1 (n=26)	P value
CR	1 (0.7)	0 (0.0)	–	1 (1.6)	0 (0.0)	–
PR	78 (53.1)	10 (28.6)	–	30 (49.2)	7 (26.9)	–
SD	56 (38.1)	19 (54.3)	–	25 (41.0)	15 (57.7)	–
PD	12 (8.2)	6 (17.1)	–	5 (8.2)	4 (15.4)	–
ORR	79 (53.7)	10 (28.6)	0.007*	31 (50.8)	7 (26.9)	0.04*
DCR	135 (91.8)	29 (82.9)	0.11	56 (91.8)	22 (84.6)	0.31

Data are presented as n (%). *, P<0.05. PSM, propensity score matching; HAIC+αPD-(L)1, HAIC-FO plus αPD-(L)1 antibody; HAIC-FO, HAIC with infusional FOLFOX regimens; HAIC, hepatic arterial infusion chemotherapy; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; αPD-(L)1, anti-programmed death-(ligand) 1 immunotherapy; SYS+αPD-(L)1, SYS plus αPD-(L)1 antibody; SYS, systemic chemotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

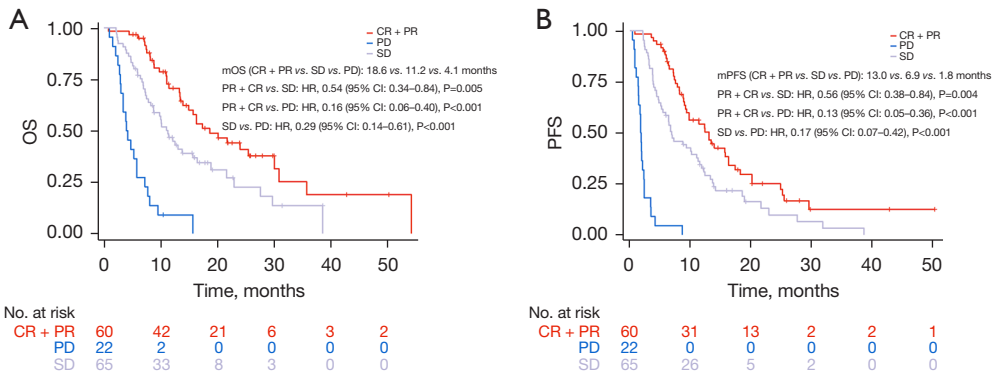

Figure 5 Kaplan-Meier survival analysis for the OS (A) and PFS (B) of CR + PR, SD, and PD groups in uICC patients receiving HAIC+αPD-(L)1 as first-line treatments. OS, overall survival; CR, complete response; PR, partial response; PD, progression disease; SD, stable disease; mOS, median OS; HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; mPFS, median PFS; uICC, unresectable intrahepatic cholangiocarcinoma; HAIC+αPD-(L)1, HAIC-FO plus αPD-(L)1 antibody; HAIC-FO, HAIC with infusional FOLFOX regimens; HAIC, hepatic arterial infusion chemotherapy; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; αPD-(L)1, anti-programmed death-(ligand) 1 immunotherapy.

ablation and 17 (17.4%) undergoing resection. There were no patients who underwent radical surgery after receiving SYS combined αPD-(L)1. Twenty-two patients who underwent radical surgery after receiving HAIC-FO combined with αPD-(L)1, 11 (50.0%) ultimately experienced recurrence, including 4 (18.2%) with intrahepatic recurrence and 7 (31.8%) with extrahepatic recurrence.

AEs

As shown in *Table 5*, the incidences of AEs in the HAIC+αPD-(L)1 and SYS+αPD-(L)1 groups were 96.7% (59/61) and 100.0% (26/26), respectively (P=0.35). The incidences of grade 1–2 and 3–4 AEs were not significantly different between the two groups (1–2 AEs: 47.5% *vs.* 65.4%, P=0.13; 3–4 AEs: 49.2% *vs.* 46.2%, P=0.80). In the HAIC+αPD-(L)1 group, the most common AEs primarily associated with hepatic toxicity were an elevated AST level (67.2%), hypoalbuminemia (47.5%), and an elevated ALT level (44.3%). In the SYS+αPD-(L)1 group, the most frequent severe AEs primarily associated with systemic toxicity were anemia (61.5%), hypertension (53.8%), and proteinuria (46.2%). Notably, HAIC+αPD-(L)1 therapy significantly reduced the incidence of grade 3–4 systemic AEs, including anemia (P=0.04), leukopenia (P=0.01), weight loss (P=0.03), and fatigue (P=0.03). No patients in either group discontinued chemotherapy due to infusion-related complications, and there were no treatment-related deaths. All recorded AEs were either self-resolving or effectively managed with medications.

Additionally, as shown in Figure S2, survival analysis was conducted on patients in the HAIC+αPD-(L)1 group based on the level of AEs, and the results showed that patients who experienced 3–4 grade AEs had no significant difference in OS and PFS compared to those who experienced 1–2 grade AEs (OS: 16.6 *vs.* 14.3 months, P=0.81; PFS: 8.9 *vs.* 10.2 months, P=0.68).

Discussion

In this study, we observed that the combination of HAIC-FO with αPD-(L)1 demonstrated a significant enhancement in treatment efficacy for uICC patients compared to SYS combined with αPD-(L)1. This was evidenced by a higher ORR, as well as prolonged PFS and OS. Moreover, HAIC-FO combined with αPD-(L)1 exhibited favorable tolerability in uICC patients. Notably, the incidence of grade 3–4 systemic AEs such as anemia, leukopenia, fatigue, and weight loss was reduced in the group receiving HAIC-FO combined with αPD-(L)1. Therefore, considering its safety and effectiveness profile, the combination of HAIC-FO with anti-PD-(L)1 therapy could be considered as a viable first-line treatment option for uICC patients.

Recently, in two large randomized clinical trials, the combination of SYS and anti-PD-(L)1 therapy has demonstrated enhanced first-line clinical efficacy in patients with advanced biliary tract cancer, including uICC (26).

Table 5 Summary of treatment-related AEs

Events	HAIC+αPD-(L)1 (n=61)			SYS+αPD-(L)1 (n=26)			P values		
	Any grade	Grade 1/2	Grade 3/4	Any grade	Grade 1/2	Grade 3/4	Any grade	Grade 1/2	Grade 3/4
Any AEs	59 (96.7)	29 (47.5)	30 (49.2)	26 (100.0)	17 (65.4)	12 (46.2)	0.35	0.13	0.80
Elevated AST	41 (67.2)	29 (47.5)	12 (19.7)	9 (34.6)	7 (26.9)	2 (7.7)	0.005*	0.07	0.16
Hypoalbuminemia	29 (47.5)	29 (47.5)	0 (0.0)	5 (19.2)	5 (19.2)	0 (0.0)	0.01*	0.01*	–
Elevated ALT	27 (44.3)	20 (32.8)	7 (11.5)	5 (19.2)	4 (15.4)	1 (3.8)	0.03*	0.10	0.26
Hypertension	27 (44.3)	21 (34.4)	6 (9.8)	14 (53.8)	13 (50.0)	1 (3.8)	0.41	0.17	0.35
Neutropenia	27 (44.3)	12 (19.7)	15 (24.6)	6 (23.1)	4 (15.4)	2 (7.7)	0.06	0.64	0.07
Anemia	27 (44.3)	25 (41.0)	2 (3.3)	16 (61.5)	12 (46.2)	4 (15.4)	0.14	0.66	0.04*
Pain abdominal	26 (42.6)	26 (42.6)	0 (0.0)	9 (34.6)	9 (34.6)	0 (0.0)	0.49	0.49	–
Leukopenia	22 (36.1)	20 (32.8)	2 (3.3)	11 (42.3)	6 (23.1)	5 (19.2)	0.58	0.37	0.01*
Thrombocytopenia	22 (36.1)	16 (26.2)	6 (9.8)	5 (19.2)	3 (11.5)	2 (7.7)	0.12	0.13	0.75
Fever	20 (32.8)	18 (29.5)	2 (3.3)	9 (34.6)	9 (34.6)	0 (0.0)	0.87	0.64	0.35
Weight loss	18 (29.5)	18 (29.5)	0 (0.0)	10 (38.5)	8 (30.8)	2 (7.7)	0.41	0.91	0.03*
Proteinuria	14 (23.0)	14 (23.0)	0 (0.0)	12 (46.2)	12 (46.2)	0 (0.0)	0.03*	0.03*	–
Vomiting	12 (19.7)	12 (19.7)	0 (0.0)	3 (11.5)	3 (11.5)	0 (0.0)	0.36	0.36	–
Elevated total bilirubin	11 (18.0)	10 (16.4)	1 (1.6)	5 (19.2)	5 (19.2)	1 (3.8)	0.90	0.75	0.53
Elevated creatinine	10 (16.4)	9 (14.8)	1 (1.6)	7 (26.9)	7 (26.9)	0 (0.0)	0.26	0.18	0.51
Fatigue	7 (11.5)	7 (11.5)	0 (0.0)	8 (30.8)	6 (23.1)	2 (7.7)	0.03*	0.17	0.03*
Dizziness	6 (9.8)	6 (9.8)	0 (0.0)	2 (7.7)	2 (7.7)	0 (0.0)	0.75	0.75	–
Elevated INR	6 (9.8)	6 (9.8)	0 (0.0)	7 (26.9)	7 (26.9)	0 (0.0)	0.04*	0.04*	–
Nausea	6 (9.8)	6 (9.8)	0 (0.0)	2 (7.7)	2 (7.7)	0 (0.0)	0.75	0.75	–
Pruritus	6 (9.8)	6 (9.8)	0 (0.0)	4 (15.4)	3 (11.5)	1 (3.8)	0.46	0.81	0.12
Abdominal distension	4 (6.6)	4 (6.6)	0 (0.0)	2 (7.7)	2 (7.7)	0 (0.0)	0.85	0.85	–
Constipation	4 (6.6)	4 (6.6)	0 (0.0)	1 (3.8)	1 (3.8)	0 (0.0)	0.62	0.62	–
Rash	4 (6.6)	4 (6.6)	0 (0.0)	2 (7.7)	2 (7.7)	0 (0.0)	0.85	0.85	–
Diarrhea	2 (3.3)	2 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.35	0.35	–

Data are presented as n (%). *, P<0.05. AE, adverse event; HAIC+αPD-(L)1, HAIC-FO plus αPD-(L)1 antibody; HAIC-FO, HAIC with infusional FOLFOX regimens; HAIC, hepatic arterial infusion chemotherapy; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; αPD-(L)1, anti-programmed death-(ligand) 1 immunotherapy; SYS+αPD-(L)1, SYS plus αPD-(L)1 antibody; SYS, systemic chemotherapy; AST, aspartate transaminase; ALT, alanine transaminase; INR, international normalized ratio.

A global phase III randomized controlled trial, known as TOPAZ-1, reported that GEMCIS chemotherapy plus durvalumab, an anti-PD-L1 antibody, as a first-line treatment for advanced biliary tract cancer significantly improved survival (mOS: 12.8 *vs.* 11.5 months, P=0.02; mPFS: 7.2 *vs.* 5.7 months, P=0.001) compared to GEMCIS chemotherapy alone (5). The KEYNOTE-966 trial, another randomized phase III study, revealed that the combination of pembrolizumab, an anti-PD-1 antibody with GEMCIS chemotherapy as a first-line therapy for patients with advanced biliary tract cancer resulted in a statistically significant and clinically meaningful improvement in OS (12.7 *vs.* 10.9 months, P=0.003) (6). In this study, patients treated with HAIC-FO combined

with anti-PD-(L)1 therapy had a mOS of 14.5 months and a mPFS of 10.4 months. These survival times were longer than those observed in the TOPAZ-1 and KEYNOTE-966 trials, suggesting that HAIC combined with anti-PD-(L)1 therapy is a promising first-line treatment option for uICC patients. Notably, the mOS of the SYS+αPD-(L)1 group in our study was comparatively lower, at only 10.5 months. A recent real-world study focusing on uICC patients reported a similar mOS of 10.7 months for SYS combined with anti-PD-(L)1 antibodies (27). Therefore, it is plausible that the results obtained from clinical trials conducted under stringent control environments and conditions may have potentially overestimated the treatment effect in actual medical practice, which could elucidate the observed lower efficacy of SYS combined with anti-PD-(L)1 antibodies in real-world studies.

Some studies have demonstrated that HAIC is effective in controlling liver disease in patients with ICC (18,28,29). In this study, we adopted IPFS because it is an important indicator for evaluating the control of intrahepatic tumors. It was found that the mIPFS in the HAIC-FO+αPD-(L)1 treatment group was significantly longer than that in the SYS+αPD-(L)1 group regardless of whether a PSM was performed (before PSM: 11.4 *vs.* 6.9 months, P<0.001; after PSM: 11.4 *vs.* 6.5 months, P<0.001). In the HAIC-FO+αPD-(L)1 group, the IPFS was longer than the PFS before (11.4 *vs.* 9.6 months) and after PSM (11.4 *vs.* 10.4 months), indicating that the combination of HAIC-FO and anti-PD-(L)1 therapy may provide a more effective control over intrahepatic lesions. In addition, subgroup analyses focusing on survival revealed that HAIC-FO combined with anti-PD-(L)1 therapy conferred a survival advantage, especially in patients with high intrahepatic tumor burden (>80 mm diameter), and without extrahepatic organ metastases, consistent with previous findings—highlighting the potential advantage of HAIC in effectively controlling intrahepatic tumors through localized treatment, thereby creating more time and opportunities for systemic therapies (28,30,31).

Historically, HAIC has made progress to some extent; however, it has faced challenges in becoming mainstream due to early technical limitations, lack of standardization, and competition from systemic therapies. Recent advancements highlight its promising future. For example, HAIC combination with systemic therapies, particularly immunotherapy, has shown survival benefits and the potential to enhance immune responses by transforming "cold tumors" into "hot tumors" (32-34). Additionally, Technological innovations, such as precise drug delivery and novel agents like nanomedicine, are expected to improve its efficacy and safety (35-37). Moreover, HAIC integration into multidisciplinary treatment (MDT) strategies as neoadjuvant or adjuvant therapy could expand its applications. With validation from large-scale clinical trials, HAIC holds great promise as a key treatment option in the era of precision medicine.

The FOLFOX regimen was selected as the chemotherapy protocol for HAIC treatment in this study, primarily based on the following considerations. First, the FOLFOX regimen has been shown to be effective and safe when administered intra-arterially in HAIC (11,13,14,38). In contrast, gemcitabine and cisplatin are generally used in SYS, and their use in HAIC is less established. Second, cisplatin is known for its nephrotoxicity and potential hepatotoxicity, which can be more pronounced when delivered directly to the liver (39). Oxaliplatin may have a more favorable safety profile for intrahepatic administration, making it a more suitable choice for HAIC in patients with compromised liver function, as is often the case in uICC. Third, several studies have investigated the use of FOLFOX in HAIC for ICC, showing promising results in terms of tumor control and survival outcomes (40-43). Finally, as this is a retrospective study, our primary objective was to assess real-world outcomes based on the existing clinical practices at our institution, where FOLFOX is the preferred regimen for HAIC in uICC patients. This choice ensures consistency in treatment protocols and allows for a more accurate evaluation of FOLFOX-based HAIC outcomes.

The findings of this study suggest that HAIC-FO may be a more suitable option, compared to SYS, when combined with anti-PD-(L)1 therapy for the treatment of uICC. This observation can potentially be attributed to various underlying mechanisms. Firstly, HAIC enhances the enrichment of chemotherapy drugs in tumors and promotes tumor cell death, leading to the release of tumor antigens and proinflammatory cytokines. The transformation of an immunosuppressed "cold tumor" into an immunogenic "hot tumor" enhances the immune response (44). Secondly, the reduction in antitumor lymphocytes that can be associated with systemic high-dose chemotherapy may potentially impact the efficacy of anti-PD-(L)1 antibodies. In contrast, the localized administration of HAIC, which typically causes less immune-system suppression, might support the antitumor activity of anti-PD-(L)1 antibodies (45). Lastly, HAIC-FO therapy, which includes oxaliplatin and 5-fluorouracil (5-FU), enhances anti-PD-(L)1 therapy by

leveraging oxaliplatin's immunogenic properties and 5-FU's reduction of tumor immunosuppression by depleting myeloid-derived suppressor cells (46-48). This combination has shown efficacy in preclinical models of colorectal and gastric cancer (49,50). In our study, most patients (73.1%) in the SYS+αPD-(L)1 group received the GEMCIS regimen (cisplatin and gemcitabine), where cisplatin is less immunogenic than oxaliplatin, and gemcitabine inhibits T-cell infiltration, potentially reducing anti-PD-(L)1 efficacy (51-53). Therefore, it is suggested that FOLFOX regimen may be more suitable for combination with anti-PD-(L)1 antibodies compared to GEMCIS. However, further preclinical studies are necessary to elucidate the underlying mechanisms guiding the treatment of uICC patients.

In addition to efficacy, safety was also investigated. Almost all patients (97.7%) experienced at least one AE. The common AEs observed in the SYS+αPD-(L)1 group were consistent with those reported in previous studies of SYS plus anti-PD-(L)1 antibodies, including elevated AST or ALT levels, anemia, leukopenia, and fatigue (5,6). Overall, there was no significant difference in the incidence of any grade AEs and grade 3–4 AEs between the HAIC+αPD-(L)1 and SYS+αPD-(L)1 treatment groups. However, it is worth noting that the HAIC+αPD-(L)1 group had a significantly lower occurrence of systemic AEs such as anemia, leukopenia, weight loss, and fatigue. One possible explanation for this disparity is that HAIC allows direct delivery of chemotherapy drugs to the liver and their clearance through the "first-pass effect", resulting in relatively low drug concentrations in peripheral blood and reduced damage to various body systems. Additionally, we performed a survival analysis of patients in the HAIC+αPD-(L)1 group based on the level of AEs, and the results showed that patients who experienced 3–4 grade AEs had no significant difference in OS and PFS compared to those who experienced 1–2 grade AEs. We consider that this may be due to effective management and supportive treatment provided after the occurrence of 3–4 grade AEs, which would not have a significant impact on the patients' long-term prognosis. These findings may encourage clinicians to continue to advance this potentially effective treatment regimen, based on close monitoring and management of AEs.

In this study, no catheter-related AEs were observed, which may be attributed to the implementation of a comprehensive set of stringent catheter management protocols at Sun Yat-sen University Cancer Center, including standardized aseptic techniques, regular checks of catheter position and function, and timely handling of potential infection risks. Moreover, the team in Sun Yat-sen University Cancer Center consists of oncologists, interventional radiologists, and nursing staff who collaborate on catheter placement, maintenance, and monitoring. However, it must be acknowledged that a small sample size may also lead to the exclusion of patients who have experienced catheter-related AEs from this study. The above factors may explain why no catheter-related AEs occurred in this study. However, it is worth noting that effective catheter management may have a learning curve, and for teams newly implementing HAIC treatment, a period of adaptation may be necessary to achieve comparable outcomes in catheter management.

There are some limitations in this study. Firstly, this was a retrospective, single-center study, which may have introduced unknown selection bias and reduced generalizability. Although we performed PSM, we were unable to eliminate all potential biases; therefore, prospective studies or randomized controlled trials are needed to confirm the results of this study. Secondly, the utilization of various types of anti-PD-(L)1 antibodies in this study might have influenced the results to some extent due to drug heterogeneity. Lastly, the limited sample size of this study, particularly after PSM implementation, led to partial data loss that could have impacted the power of efficacy assessment.

Conclusions

In summary, the study suggests that HAIC-FO combined with anti-PD-(L)1 therapy may be more effective than SYS combined with anti-PD-(L)1 therapy in improving outcomes for patients with uICC, while maintaining an acceptable safety profile. These findings could offer valuable insights to inform treatment decisions in clinical practice. However, prospective randomized controlled studies are necessary to further elucidate the potential role of HAIC-FO combined with anti-PD-(L)1 antibody therapy in uICC patients.

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Footnote

Reporting Checklist: The authors have completed the

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Review Committee of the Sun Yat-sen University Cancer Center (No. G2024-080-01), and individual consent for this retrospective analysis was waived.

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