Supplementary tables

Supplementary Table 1 Prognostic factor analysis for overall survival

Variable	Univariable	Multivariable
Age, years		
≤ 65	Ref	
> 65	1.03 (0.41-2.59, p=.942)	
Gender		
Female	Ref	
Male	1.48 (0.59-3.71, p=.403)	
Comorbidity		
Absence	Ref	Ref
Presence	2.27 (1.14-4.51, p=.019)	2.10 (1.03-4.28, p=.041)
HBV		
Absence	Ref	
Presence	0.44 (0.15-1.23, p=.116)	
Ascites		
Absence	Ref	Ref
Presence	1.40 (1.17-1.68, p<.001)	1.70 (0.91-3.17, p=.097)
ALBI grade		
1	Ref	Ref
2-3	2.22 (1.31-3.76, p=.003)	1.67 (0.95-2.92, p=.075)
HCC diameter, cm		
< 5	Ref	
5-10	1.19 (0.36-3.95, p=.777)	
>10	1.10 (0.33-3.61, p=.876)	
HCC number		
1-3	Ref	Ref
>3	3.15 (1.75-5.69, p<.001)	2.78 (1.51-5.14, p=.001)
Vascular invasion		

Absence	Ref	
Presence	1.42 (0.70-2.91, p=.334)	
Metastasis		
Absence	Ref	Ref
Presence	1.94 (1.14-3.32, p=.015)	1.76 (0.99-3.13, p=.055)
TRIPLET protocol		
TRIPLET	Ref	Ref
TRIPLET-MWA	0.17 (0.08-0.33, p<.001)	0.16 (0.08-0.33, p<.001)

A Cox proportional hazards regression model for overall survival was used. All variables were included in a multivariate stepwise Cox regression analysis. Only the variables with a $P < 0.05$ in the final model were presented. HR, hazard ratio; CI, confidence intervals; PS, performance status; HBV, hepatitis B virus; ALBI, albumin - bilirubin ; AFP: α-fetoprotein; MWA, microwave ablation.

Supplementary Table 2 Prognostic factor analysis for progression-free survival

Variable	Univariable	Multivariable
Age, years		
≤ 65	Ref	
> 65	0.99 (0.55-1.79, p=.976)	
Gender		
Female	Ref	
Male	1.30 (0.76-2.22, p=.341)	
Comorbidity		
Absence	Ref	
Presence	1.41 (0.85-2.33, p=.189)	
HBV		
Absence	Ref	

Presence	0.54 (0.28-1.03, p=.061)	
Ascites		
Absence	Ref	Ref
Presence	1.32 (1.04-1.66, p=.020)	1.09 (0.71-1.69, p=.688)
ALBI grade		
1	Ref	
2-3	1.26 (0.90-1.76, p=.182)	
HCC diameter, cm		
< 5	Ref	
5-10	0.57 (0.28-1.17, p=.127)	
>10	0.84 (0.42-1.66, p=.609)	
HCC number		
1-3	Ref	Ref
>3	1.82 (1.30-2.55, p<.001)	1.60 (1.13-2.27, p=.008)
Vascular invasion		
Absence	Ref	
Presence	1.07 (0.71-1.62, p=.738)	
Metastasis		
Absence	Ref	Ref
Presence	1.81 (1.30-2.51, p<.001)	1.86 (1.32-2.62, p<.001)
TRIPLET protocol		
TRIPLET	Ref	Ref
TRIPLET-MWA	0.57 (0.41-0.80, p=.001)	0.52 (0.37-0.74, p<.001)

A Cox proportional hazards regression model for overall survival was used. All variables were included in a multivariate stepwise Cox regression analysis. Only the variables with a $P < 0.05$ in the final model were presented. HR, hazard ratio; CI, confidence intervals; PS, performance status; HBV, hepatitis B virus; ALBI, albumin - bilirubin ; AFP:α-fetoprotein; MWA, microwave ablation.

Supplementary Table 3 Prognostic factor analysis for overall survival in TRIPLET-MWA group

Variable	Univariable	Multivariable
Age, years		
≤ 65	Ref	
> 65	0.91 (0.11-7.23, p=.926)	
Gender		
Female	Ref	
Male	1.68 (0.21-13.27, p=.623)	
Comorbidity		
Absence	Ref	
Presence	3.12 (0.65-15.08, p=.157)	
HBV		
Absence	Ref	Ref
Presence	0.03 (0.00-0.33, p=.004)	0.10 (0.01-0.99, p=.049)
Ascites		
Absence	Ref	
Presence	2.58 (0.55-12.20, p=.232)	
ALBI grade		
1	Ref	Ref
2-3	4.10 (1.00-16.75, p=.050)	2.56 (0.60-10.95, p=.204)
HCC diameter, cm		
< 5	Ref	
5-10	0.68 (0.08-6.08, p=.729)	
>10	0.47 (0.05-4.01, p=.487)	
HCC number		
1-3	Ref	
>3	1.86 (0.47-7.31, p=.376)	
Vascular invasion		

Absence	Ref	
Presence	0.54 (0.15-1.92, p=.339)	
Metastasis		
Absence	Ref	
Presence	2.64 (0.67-10.40, p=.165)	
Ablation		
Incomplete	Ref	Ref
Complete	0.13 (0.03-0.61, p=.010)	0.17 (0.03-0.87, p=.033)

A Cox proportional hazards regression model for overall survival was used. All variables were included in a multivariate stepwise Cox regression analysis. Only the variables with a P < 0.05 in the final model were presented. HR, hazard ratio; CI, confidence intervals; PS, performance status; HBV, hepatitis B virus; ALBI, albumin - bilirubin ; AFP:α-fetoprotein; MWA, microwave ablation.

Supplementary Table 4 Prognostic factor analysis for progression-free survival in TRIPLET-MWA group

Variable	Univariable	Multivariable
Age, years		
≤ 65	Ref	
> 65	1.23 (0.53-2.87, p=.626)	
Gender		
Female	Ref	
Male	1.12 (0.55-2.27, p=.757)	
Comorbidity		
Absence	Ref	
Presence	1.55 (0.70-3.42, p=.277)	
HBV		
Absence	Ref	Ref

Presence	0.15 (0.04-0.63, p=.010)	0.26 (0.06-1.19, p=.083)
Ascites		
Absence	Ref	
Presence	0.63 (0.23-1.75, p=.377)	
ALBI grade		
1	Ref	
2-3	0.41 (0.06-2.96, p=.376)	
HCC diameter, cm		
< 5	Ref	Ref
5-10	1.74 (1.04-2.90, p=.035)	1.61 (0.94-2.76, p=.082)
>10		
HCC number	Ref	
1-3	0.50 (0.17-1.49, p=.215)	
>3	0.70 (0.25-1.96, p=.497)	
Vascular invasion		
Absence	Ref	Ref
Presence	1.72 (1.00-2.97, p=.050)	1.62 (0.91-2.88, p=.099)
Metastasis		
Absence	Ref	
Presence	1.11 (0.61-2.03, p=.727)	
Variable		
Age, years	Ref	
≤ 65	1.11 (0.67-1.85, p=.679)	
Ablation		
Incomplete	Ref	Ref
Complete	0.25 (0.15-0.42, p<.001)	0.29 (0.17-0.49, p<.001)

A Cox proportional hazards regression model for overall survival was used. All variables were included in a multivariate stepwise Cox regression analysis. Only the variables with a $P < 0.05$ in the final model were presented. HR:

hazard ratio; CI: confidence intervals; PS: performance status; HBV: hepatitis B virus; ALBI: albumin - bilirubin; AFP: α-fetoprotein; MWA: microwave ablation

Supplementary Table 5 Survival Comparison between TRIPLET group versus TRIPLET-MWA group according to Analytic Methods

Analysis	HR	95%CI	*P* value
OS			
Unadjusted	0.17	0.08-0.33	< 0.001
Adjusted†	0.17	0.08-0.35	< 0.001
IPTW	0.20	0.10-0.41	< 0.001
PSM	0.22	0.10-0.49	< 0.001
PFS			
Unadjusted	0.57	0.41-0.80	0.001
Adjusted‡	0.53	0.38-0.75	< 0.001
IPTW	0.58	0.41-0.83	0.002
PSM	0.57	0.38-0.85	0.005

* HRs for the HAIC group compared with the TACE group.

† Adjusted for HBV, OR to the first HAIC, and serum AFP level, which were significant in the univariate analysis.

‡ Adjusted for comorbidity, HBV, HCC_diameter, OR to the first HAIC, and serum AFP level, which were significant in the univariate analysis.

* Adjusted for

HAIC, hepatic arterial infusion chemotherapy; TACE, transarterial chemoembolization; IPTW, inverse probability treatment weighting; PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; OS: overall survival; PFS: progression-free survival; IPFS: intrahepatic progression-free survival.

Supplementary Table 6 Adverse Events Between HAIC-SR group and HAIC-

MWA group

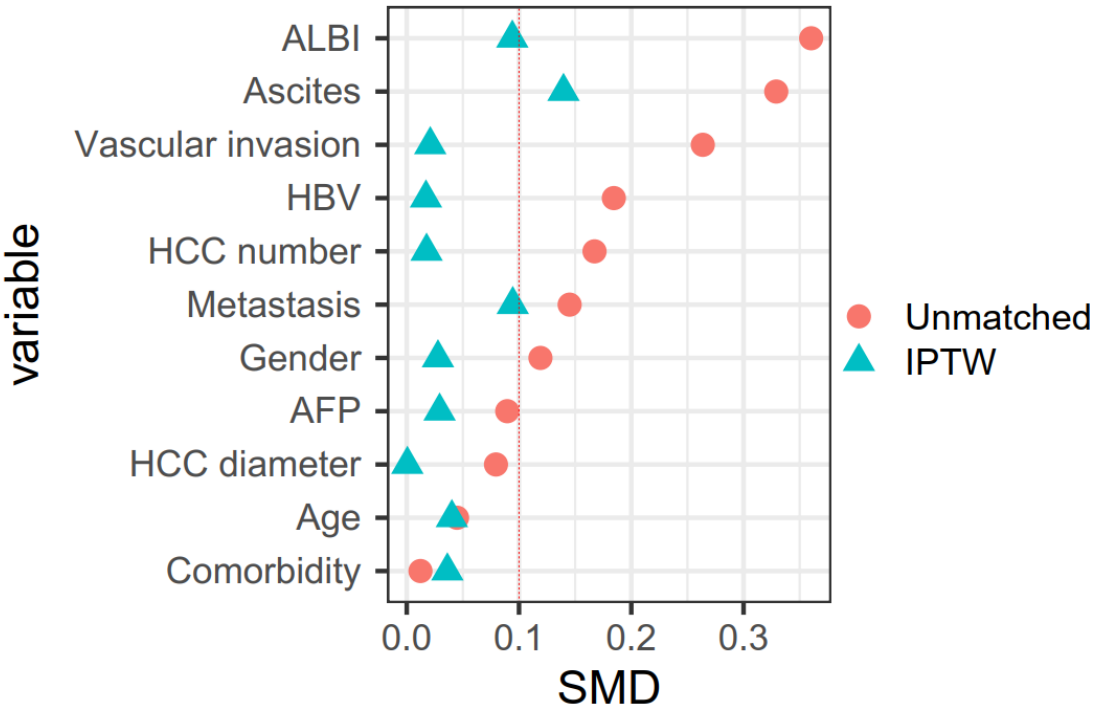
Adverse events	T-A group (n=82)		T-M group (n=82)			
	Grade 1-2	Grade 3-4	Grade 1-2		Grade 3-4	
	n (%)	n (%)	n (%)	*P value*	n	*P*
Total	38 (46.3)	8 (9.8)	43 (52.4)	0.874	10 (3.8)	0.936
Blood/bone marrow suppression						
Leukopenia	5 (6.0)	1 (1.2)	-	0.162	1 (1.2)	1.000
Neutropenia	2 (2.1)	-	-	1.000	-	1.000
Reduced hemoglobin	1 (1.2)	-	-	1.000	-	1.000
Coagulation disorder	NA	-	-	1.000	-	1.000
Elevated INR	3 (3.6)	-	1 (1.2)	1.000	-	1.000
Constitutional symptom						
Weight loss	21 (21.6)	-	6(7.2)	0.116	-	1.000
Fever	14 (14.3)	-	6(7.2)	0.592	-	1.000
Fatigue	9 (9.3)	-	3(3.6)	0.541	-	1.000
GI disorder						
Ascites	10 (10.3)	-	2 (3.8)	0.215	1 (1.2)	1.000
Diarrhea	4 (4.8)	-	1 (1.2)	0.657	-	1.000
Anorexia	3 (3.6)	-	1 (1.2)	1.000	-	1.000
Constipation	2 (2.4)	-	-	1.000	-	1.000

Vomiting	4 (4.8)	-	3 (3.6)	0.998	-	1.000
Pain						
Abdominal nonspecific	1 (1.2)	1 (1.2)	-	1.000	-	1.000
Right shoulder back	1 (1.2)	-	1(1.2)	1.000	-	1.000
Laboratory abnormalities						
Elevated ALT	11 (11.3)	2 (2.1)	11 (11.3)	0.119	-	1.000
Elevated AST	12 (14.4)	1 (1.0)	8 (9.6)	0.639	-	1.000
Elevated TBIL	10 (12.2)	-	6 (7.2)	0.848	-	1.000
Elevated creatinine	8 (8.2)	-	1 (1.2)	0.160	-	1.000
Anaemia	NA	-	NA	1.000	-	1.000
Others	3 (3.6)	-	5 (6.1)	0.131	-	1.000

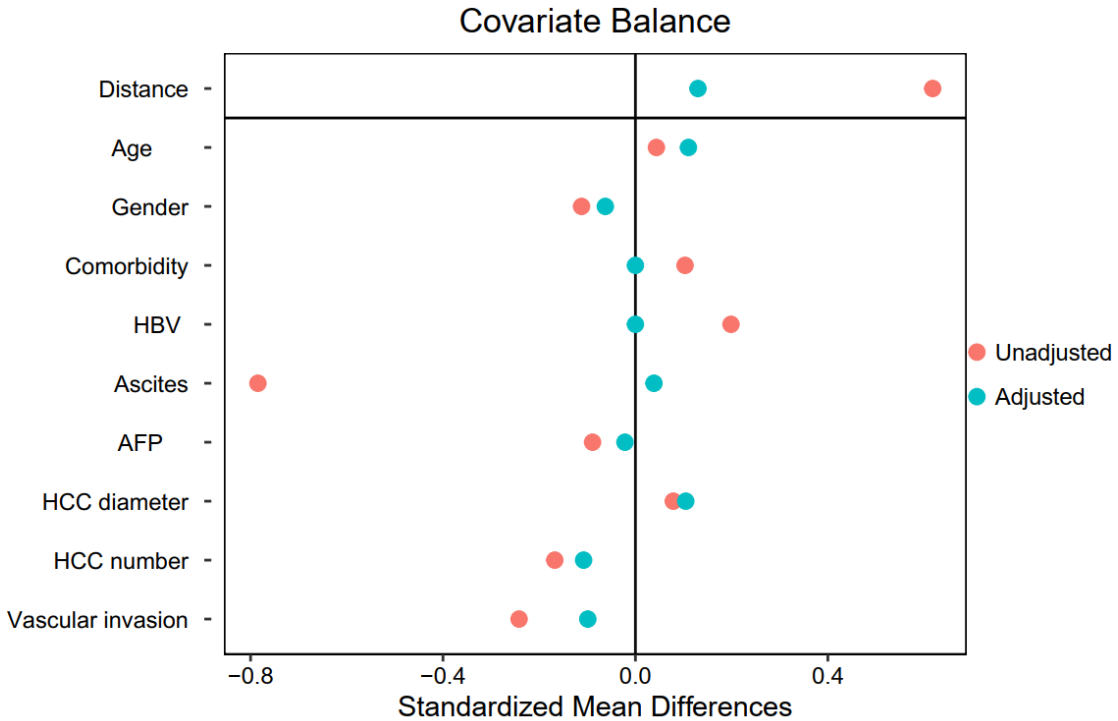
Note-Data in bracket was percent of patients. The data in two groups were compared by using the Chi square test or Fisher's exact test.

HAIC, hepatic arterial infusion chemotherapy; SR, surgical resection; MWA, microwave ablation; ALT, alanine aminotransferase; AST, aspartate aminotransferase, GI=gastrointestinal; INR, international normalized ratio; TBIL, total bilirubin.

Supplementary figure



Supplementary Figure 1 Distribution of the propensity score after matching for all patients.



Supplementary Figure 2 Distribution of the inverse probability treatment weighting after adjusting for all patients.

Supplementary document

E1.1 TRIPLET Protocol

HAIC

Patients received HAIC plus TKIs plus PD-1 inhibitors in 21-day cycles until disease progression and unacceptable toxicity. For the HAIC procedure, a 5 French Yashiro or right hepatic catheter was inserted through the femoral artery with a 2.7 French microcatheter inside the tip of the microcatheter that was in the tumor feeding artery on day 1 in every cycle of treatment[1-3]. The location of the tip was dependent on the arterial supply of the tumor identified by arteriography: right/left hepatic artery for tumors in the right/left lobe and the proper hepatic artery for tumors in two lobes. When the tumor simultaneously accepts blood supply from extrahepatic arteries, such as the celiac trunk or the superior mesenteric artery, the tip is in the superior feeding artery, and the subsuperior arteries are embolized. If necessary, the gastroduodenal artery was embolized by coil embolization.

Administration of medication began within three days of catheter insertion. The therapeutic scheme was a modified FOLFOX7 regimen, including oxaliplatin (85 mg/m2 infusion for three hours on day 1), leucovorin (400 mg/m^2 for 2 hours from hours 4 to 5 on day 1) and fluorouracil (2,500 mg/m^2 continuous 46-hour infusion on days 1 to 3). All chemotherapeutic agents were delivered via HAIC. The catheter and sheath were removed after the completion of HAIC and reinserted for the next HAIC cycle.

TKI therapy

TKI therapy was continuously administered from day 8 of the first cycle until progressive disease or unacceptable toxicity occurred. Apatinib (AiTan, 250 mg once daily, Jiangsu Hengrui Medicine Co. Ltd), a selective VEGFR2 inhibitor, was selected for this combination therapy in 20 patients because it is approved as a second-line therapy for advanced HCC in China. Additionally, apatinib has shown synergistic antitumor effects in vivo in combination with immune

checkpoint inhibitors. Additionally, lenvatinib (8 mg once daily, Eisai Europe Ltd.) was administered in two patients.

PD-1 inhibitor therapy

PD-1 inhibitor treatment was started on day 4 of each 21-day cycle, beginning with the second cycle, until progressive disease or unacceptable toxicity. The administered PD-1 inhibitors in this study included toripalimab (JS001, 240 mg once every 3 weeks, Shanghai Junshi Biosciences Co., Ltd.), a humanized IgG4 mAb against PD-1 monoclonal antibody; camrelizumab (AiRuiKa™, 200 mg once every 3 weeks, Jiangsu Hengrui Medicine Co. Ltd), a humanized high-affinity IgG4-kappa anti-PD-1 monoclonal antibody [33]; tislelizumab (BaiZeAn®, 200 mg once every 3 weeks), a humanized IgG4 mutation with low affinity for the Fc-γ receptor 1 (FcγR1) mAb against PD-1; and sintilimab (Tyvyt®, 200 mg once every 3 weeks, Innovent Biologics [Suzhou] Co., Ltd), a fully human IgG4 anti-PD-1 mAb against PD-1 monoclonal antibody.

E1.2 Criteria for protocol treatment discontinuation

A) Tumor progression

Progressive disease (PD) was assessed by dynamic CT or MRI based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST).

B) Intolerable adverse event

i) The patient could not resume HAIC after 30 days of interruption due to an adverse event;

ii) An adverse event meeting the criteria for HAIC dose reduction occurred after the dose was already reduced to the lowest level;

iii) Life-threatening adverse event;

C) The need for another anticancer treatment due to downstaging at the physician's discretion;

D) HAIC became technically infeasible;

E) The patient requested to be withdrawn from the study;

F) Death.

E1.3 MWA therapy

A 64 multidetector-row CT (MDCT) scanner (Brilliance CT BigBore; Phillips Medical Systems, The Netherlands) was used to guide percutaneous MWA for intrahepatic HCC and extrahepatic metastasis. MWA was performed by three interventional radiologists (Y.K.G., M.X.Z. and P.H.W.) with at least 5 years of experience in MWA. A 2-cm skin incision was made with a scalpel, and local analgesia was achieved by intravenous administration of remifentanil (2-3 ng/ml target concentration infusion) and local injection of 5-15 ml of 1% lidocaine. The MW antenna was in the tumor, and the deployment degree scale was determined according to the tumor size and shape. Each tumor was ablated commonly with 1-2 antennas, but larger tumors or multiple tumors could be ablated with 3 antennas according to the actual situation. Patients laid either in a supine or a prone position on the scanning bed according to the location of the lesions. After anesthesia, a 15-gauge, 18-cm MWA antenna (MTC-3C, Nanjing Qinghai Research Institute of Microwave Electric, China) was inserted into the tumor at a predetermined angle. To ensure the appropriate position of the MW antenna, CT image scanning was performed again before MWA. The power settings and ablation times were determined according to the standard recommendations provided by the manufacturer of the equipment. Each MWA session used an overlapping technique to ensure the eradication of the entire tumor, and a 5 mm safe margin should be achieved as much as possible. For patients with large tumors (maximum diameter > 5 cm) or multiple tumors, the strategy of multiple sessions of ablation could be adopted if complete ablation could not be obtained at once. The following measures were enacted to avoid ablative ambustion: (1) 0.9% saline was injected to separate the liver from other vital organs; (2) a temperature probe was inserted to measure the ablation temperature in real time.

E1.4 Clinical data selection

16 clinical variables are collected as follows: (1) demographic and history variables (ECOG, age, gender, comorbidities (i.e., hypertension, diabetes, heart disease, renal disease a esophageal gastric varices, etc.), etiology, ALBI grade, ascites); (2) tumor features (maximal tumor diameter, number of tumor); (3) laboratory findings (α-fetoprotein [AFP], serum albumin; [ALB], serum total bilirubin [STB], platelet counts, prothrombin time (PT), international normalized ratio [INR], aspartate aminotransferase [AST] and alanine aminotransferase [ALT]). Albumin- bilirubin (ALBI) grades were used to replace CTP grade for their objectiveness. ALBI score was calculated before treatment using the appropriate clinical parameters and ALBI grade was defined as follows: (log 10 bilirubin [BI] [μ mol /L] × 0.66) + (albumin [AL] [g/L] ×-0.085), (grade 1, 2, and 3 = ≤ -2.60, > -2.60 to -1.39, and > -1.39, respectively) [4].

References

[1] Kudo M, Ueshima K, Chan S et al. Lenvatinib as an Initial Treatment in Patients with Intermediate-Stage Hepatocellular Carcinoma Beyond Up-To-Seven Criteria and Child-Pugh A Liver Function: A Proof-Of-Concept Study. Cancers (Basel) 11.

[2] Zhu K, Huang J, Lai L et al. Medium or Large Hepatocellular Carcinoma: Sorafenib Combined with Transarterial Chemoembolization and Radiofrequency Ablation. Radiology 288:300-307

[3] Shi F, Wu M, Lian SS et al. Radiofrequency Ablation Following Downstaging of Hepatocellular Carcinoma by Using Transarterial Chemoembolization: Long-term Outcomes. Radiology 293:707-715

[4] Ni JY, Fang ZT, An C, et al. Comparison of albumin-bilirubin grade, platelet-albumin-bilirubin grade and Child-Turcotte-Pugh class for prediction of survival in patients with large hepatocellular carcinoma after transarterial

chemoembolization combined with microwave ablation. Int J Hyperthermia 2019;36:841-853.