Journal of Hepatocellular Carcinoma

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ORIGINAL RESEARCH

High-Risk Hepatocellular Carcinoma: Hepatic Arterial Infusion Chemotherapy versus Transarterial Chemoembolization

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Objective: To compare the efficacy and safety of hepatic arterial infusion chemotherapy (HAIC) with transarterial chemoembolization (TACE) for the treatment of high-risk hepatocellular carcinoma (hHCC) patients.

Methods: Between January 2014 and August 2022, a total of 1765 consecutive patients with hHCC who underwent initial intra-arterial therapies were reviewed and divided into a TACE group (n, 507) and a HAIC group (n, 426). The study used propensity score matching (PSM) to reduce selectivity bias. Overall survival (OS) and progression-free survival (PFS) were compared using Kaplan–Meier curves with the Log rank test. The objective response rate (ORR), conversion surgery rate (CSR) adverse event (AE) comparison and subgroup analysis were performed between the two groups.

Results: After PSM 1:1, 444 patients were divided into two groups. The patients with hHCC who received HAIC had higher median PFS (6.1 vs 3.3 months, $P < 0.001$) and OS (10.3 vs 8.2 months, $P=0.303$) than TACE. Higher ORR (24.8% vs 11.7%) and CSR (15.5% vs 8.9%) were found in the HAIC group than in the TACE group (both $P < 0.05$). The incidence of grade 3/4 AE was 23.9% and 8.1% in the TACE and HAIC groups, respectively. The subgroup analysis suggest that HAIC appeared to particularly benefit patients with tumor diameter of more than 10 centimeters (hazard ratio [HR], 0.6; 95% CI, 0.47–0.77; p, 0.00) and PVTT Vp4 (HR, 0.56; 95% CI, 0.39–0.8; *P*, 0.01) for PFS outperforming TACE.

Conclusion: HAIC can provide better disease control for hHCC than cTACE, with a comparable long-term OS and safety.

Keywords: hepatocellular carcinoma, transarterial chemoembolization, hepatic artery infusion chemotherapy, high risk

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related mortality worldwide,[1] and a large proportion of patients are in advanced stages at the time of diagnosis, with a poor prognosis, especially for patients with the combination of portal vein tumor thrombosis (PVTT),[2–4] bile duct invasion or large HCC with high tumor burden.[5] Previously, the IMbrave150 study defined combined Vp4 portal vein embolization, bile duct invasion, and tumor infiltration volume of more than 50% as high risk,[6] but significant challenges remain in the treatment of these populations.

Transarterial chemoembolization (TACE) is recommended for the treatment of advanced HCC according to the National Comprehensive Cancer Network (NCCN) and China Liver Cancer Staging (CNLC) guidelines, including the

Received: 31 January 2024
Accepted: 20 March 2024
Published: 27 March 2024

BRIDGE study, which showed that TACE is a commonly used therapy for the treatment of advanced HCC.[7] However, the Barcelona Clinic Liver Cancer (BCLC) staged treatment algorithm endorsed by the American Association for the Study of Liver Diseases (ASLD) and the European Association for the Study of the Liver (EASL) do not recommend TACE for patients with PVTT.[5,8] VP4 in particular remains a relative contraindication to TACE due to the potential risk of causing hepatic infarction or hepatic impairment.[9] In patients with a high tumor burden, TACE remains the standard of care in this group. However, the rate of complete tumor remission is significantly lower when the tumor diameter is beyond 7 cm, and the overall survival (OS) is only 11.2–13.2 months. The unsatisfactory effect of TACE may be due to the difficulty of complete embolization and the susceptibility to TACE resistance, as well as the use of large amounts of embolic particles, which increases the incidence of adverse effects, such as deterioration of liver reserve function, postembolization syndrome, and off-target embolization.[10–12]

Hepatic arterial infusion chemotherapy (HAIC) delivers sustained high concentrations of chemotherapeutic agents locally to the tumor compared to TACE, is superior to intravenous administration and does not require large amounts of embolic particles for embolization, reducing the risk of developing adverse events during treatment.[13] The median OS of HAIC in patients with advanced HCC ranges from 6.9 to 17.6 months, with efficacy rates ranging from 12.2% to 52%. Previous studies of HAIC in patients with advanced HCC with PVTT have shown remission and disease control rates of 33–52% and 47%-77%, respectively.[3,14–16] Moreover, a randomized study showed that patients receiving sorafenib with HAIC for PVTT had a significantly longer median OS and PFS than patients receiving sorafenib alone (OS of 14.9 months vs 7.2 months, $P= 0.012$).[17] The results from a Phase III randomized study of giant HCC (≥7 cm) showed a prolonged median OS in the FOLFOX-HAIC group compared to the TACE group (23.1 vs 16.1 months, $P<0.001$).[18]

To date, HAIC and TACE, which prolong the survival duration of patients with high-risk HCC (hHCC), are still controversial. Herein, the aim of this study was to investigate the effectiveness and safety of HAIC vs TACE for the treatment of hHCC based on a large sample size from multiple centers in this real-world study.

Materials and Methods

The study was conducted in accordance with the Declaration of Helsinki. Approval was obtained from the institutional review boards and/or independent ethics committees of the participating institutions (2023-LHKY-122-02).

Study Design and Patients

This study is a multicenter, retrospective, observational cohort study that included 1765 patients with unresectable HCC who were diagnosed with high-risk factors and received initial intra-arterial therapies (IATs) between January 1, 2014, and August 31, 2022, at eight medical centers in China. The IATs procedures, patients inclusion and exclusion criteria are described in Supplementary Information E1.1–1.2 The decision making was mainly made by the patients and their families based on the recommendations made by the multidisciplinary treatment (MDT) team consisting of interventional oncologists, medical oncologists and surgical oncologists, and all enrolled patients signed an informed consent form.

Follow-Up and Assessment

Patients were routinely followed until death or the end of the study (August 30, 2023). Patient evaluations were scheduled prior to each treatment visit or during each routine follow-up visit, at least 3–4 weeks apart. At each visit, an assessment was performed according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, published by the US Department of Health and Human Services; all adverse events were documented and evaluated; and standard laboratory tests were completed (complete blood count, biochemistry, coagulation, and urinalysis). Patients received follow-up with contrast-enhanced CT/MRI every 6–9 weeks. The imaging of the patients' responses to oncologic therapy was independently reviewed and interpreted according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria by two physicians with extensive experience in diagnostic abdominal imaging as described above. In case of disagreement between the two evaluations, a consensus conclusion was reached.

Endpoints

The response to IATs was assessed by dynamic contrast-enhanced CT or magnetic resonance imaging (MRI) based on the mRECIST and included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), and the imaging was performed every 4–6 weeks after the initial IAT and evaluated independently by two radiologists (reader 1, P.Y.W., and reader 2, Y.K., with 10 years of experience) who were blinded to the IAT procedures at the time of data collection. In this study, we compared three endpoints between the TACE group and the HAIC group. The primary endpoints were OS and progression-free survival (PFS). The second endpoints were the ORR, disease control rate (DCR) and conversion surgery rate (CSR). The definitions of endpoints are shown in the Supplementary Information E1.3. The third endpoint was AEs occurring after the ITA procedure, and the AEs were evaluated based on Common Terminology Criteria for Adverse Events v4.0. Assessments.

Statistical Analysis

All statistical analyses in this study were performed using R (version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria) and SPSS Statistics version 23.0 (IBM Corp.). To eliminate the problem of imbalance of confounders between the groups, PSM analysis was performed using a 1:1 radius matching method (0.05) with no put-back sampling and a caliper value of 0.05. The median and IQR were used for continuous variables, and frequencies and proportions were used for categorical variables. The *t*-test or Mann–Whitney *U*-test was used to analyze continuous variables. The chi-squared test or Fisher's exact test was used to analyze categorical variables. The Log rank test was used to compare the differences in PFS and OS between the two groups. Survival curves were plotted using the Kaplan–Meier method. Univariate and multivariate analyses were performed using the Cox proportional hazards model with a forward procedure for propensity-matched samples. Forest plots were used to display these data. Subgroup analyses were planned for the prespecified subgroups to compare PFS and OS between the two groups. In addition, differences in PFS and OS between the groups were assessed using multivariate Cox proportional hazards models for all patients who were not matched. A two-tailed P value <0.05 was considered statistically significant.

Results

Baseline Characteristics of the Patients

Figure 1 illustrates the enrollment pathway for patients with hHCC. Finally, a total of 933 hHCC patients were screened and enrolled in this study, with 507 patients in the TACE group and 426 in the HAIC group. Table 1 lists the baseline characteristics of the patients stratified according to treatment modality, there are 42 females and 402 males (mean age, 52.53 ± 11.7 years). A total of 72.0% of patients were in BCLC stage C, 93.4% of patients had a history of hepatitis B virus, 73.6% of patients had a maximum tumor diameter of >10 cm, and 58.2% of patients had PVTT, of which Vp4 accounted for 40.9% of the patients. After matching the first two groups based on the ECOG score, BCLC stage, complications, cirrhosis, maximum tumor diameter, number of tumors, PVTT, hepatic vein thrombus, and extrahepatic metastasis, the difference was statistically significant (all, $P < 0.05$), and the balance of the distribution of the general clinical information between the groups was poor. After using the PSM (1:1) to match patients with the most similar propensity scores of the two groups, the result was that the two groups were successfully matched to 222 pairs of patients, and all the variables were not significantly statistically significant ($P>0.1$) after matching.

Survival Comparsion

Before 1:1 matching (Figure 2a and b), HAIC group patients had a median PFS of 5.7 months (95% CI, 4.9–6.5), significantly longer than the 4.1 months (95% CI, 3.6–5.0) in the TACE group (P=0.047). However, the difference in median OS between the two groups, 9.2 months (95% CI, 8.6–9.9) for HAIC and 8.8 months (95% CI, 8.0–10.5) for TACE, was not statistically significant (P=0.054).

After 1:1 matching (Figure 2c and d), the median follow-up was 10.3 months for TACE and 8.2 months for HAIC. The median PFS for HAIC patients increased to 6.1 months (95% CI, 5.1–7.5), significantly longer than the 3.3 months (95% CI, 2.9–4.3) in the TACE group (P=0.000). Again, the difference in median OS, 10.3 months (95% CI, 9.1–12.0) for HAIC and 8.2 months (95% CI, 7.2–9.4) for TACE, was not statistically significant (P=0.303).

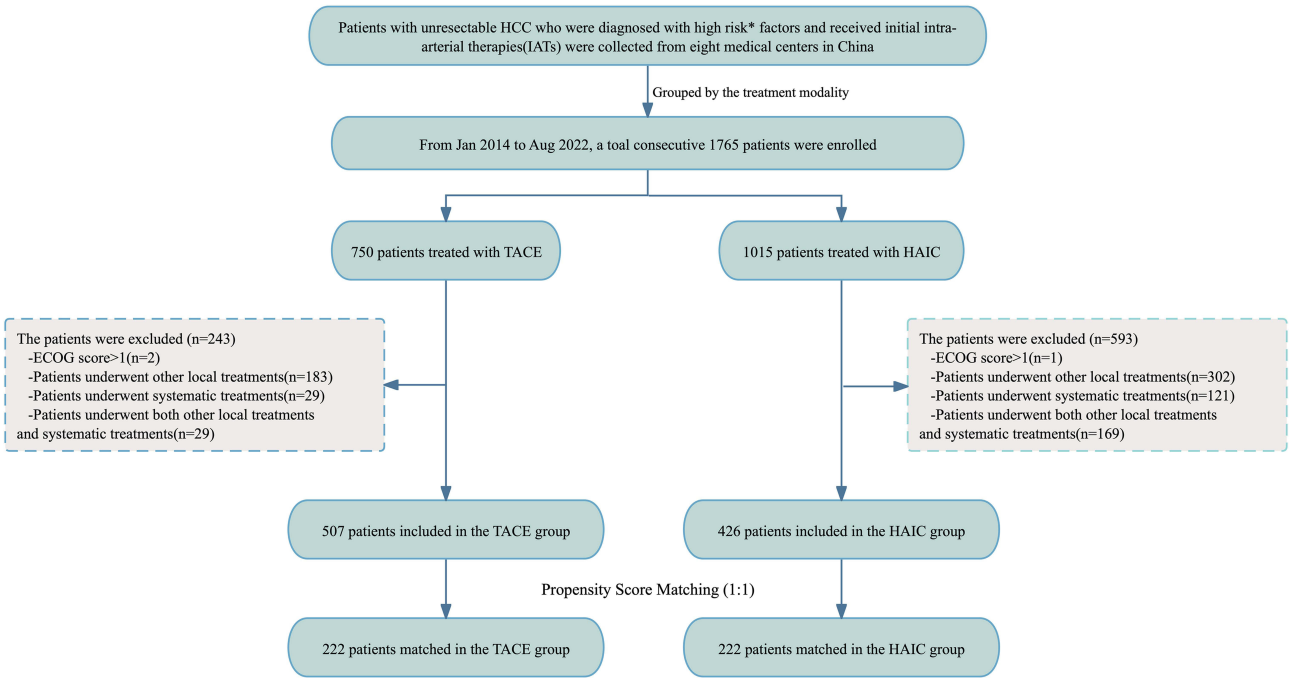

Figure 1 Enrollment pathway of patients with high-risk hepatocellular carcinoma(hHCC) who underwent HAIC and TACE therapy. *High risk: patients with Vp4 portal vein tumor thrombosis (PVTT), bile duct invasion, or a tumor infiltration volume of more than 50%.
Abbreviations: HCC, hepatocellular carcinoma; HAIC, hepatic arterial infusion chemotherapy; TACE, transarterial chemoembolization.

Efficacy

The tumor responses of patients in the TACE and HAIC groups are shown in Table 2. According to the mRECIST criteria, the ORR was higher in the HAIC group (24.8% vs 11.7%, P <0.001) than in the TACE group. the CSR of patients in the HAIC group (15.5% vs 8.9%, P <0.05) was also significantly higher than that of patients in the TACE group. The DCR of patients in the HAIC group (83.8% vs 57.7%, P=0.000) was also significantly higher than that of patients in the TACE group.

Univariate and Multivariate Analyses

Univariate and multivariate analyses assessed risk factors for PFS and OS (Table 3). After adjusting for potential confounders, several factors were associated with improved PFS, including ECOG score (0,1) (HR, 0.48, 95% CI, 0.27–0.85, P=0.011) and treatment modality (TACE, HAIC) (HR, 0.61, 95% CI, 0.49–0.75, P<0.001). Complications (absence, presence) (HR, 0.63, 95% CI, 0.43–0.92, P=0.016) was an independent protective factor for OS.

Subgroup Analysis

A subgroup analysis of PFS and OS according to clinical variables (forest plot) is shown in Figure 3 below. Irrespective of the presence or absence of microvascular invasion extrahepatic metastases and tumor number, HAIC provided a clear clinical benefit in terms of PFS in the following subgroups: age less than or equal to 65 years (HR 0.64, 95% CI 0.51–0.8, P= 0.00), male (HR 0.64, 95% CI 0.51–0.8, P= 0.00), no hepatitis (HR 0.64, 95% CI 0.51–0.79, P= 0.00), ECOG 0 (HR 0.62, 95% CI 0.5–0.76, P=0.00), Child–Pugh A (HR 0.64, 95% CI 0.52–0.79, P=0.00), BCLC C (HR 0.58, 95% CI 0.44–0.76, P=0.00), tumor diameter of more than 10 centimeters (HR 0.6, 95% CI 0.47–0.77, P=0.00), no hepatic vein cancerous embolism (HR 0.65, 95% CI 0.52–0.80, P=0.00), PVTT Vp4 (HR 0.56, 95% CI 0.39–0.8, P=0.00), and no PVTT (HR 0.56, 95% CI 0.39–0.8, P= 0.01). However, in terms of OS, clinical benefit was seen only in patients with PVTT Vp1-3 (HR 0.12, 95% CI 0.02–0.65, P=0.01).

Table 1 Baseline Characteristics of the Patients with HCC Who Received TACE and HAIC Therapy Before and After PSM

Characteristic	Before PSM			After PSM		
	TACE (N=507)	HAIC (N=426)	P-value	TACE (N=222)	HAIC (N=222)	P-value
Age Median age, mean ± SD	54.00±12.02	51.71±11.90	0.004	52.79±11.71	52.27±11.72	0.644
≤65	414 (81.7%)	368 (86.4%)	0.062	189 (85.1%)	191 (86.0%)	0.893
>65	93 (18.3%)	58 (13.6%)		33 (14.9%)	31 (14.0%)	
Sex						
Female	57 (11.2%)	43 (10.1%)	0.646	19 (8.6%)	23 (10.4%)	0.627
Male	450 (88.8%)	383 (89.9%)		203 (91.4%)	199 (89.6%)	
ECOG						
0	489 (96.4%)	388 (91.1%)	<0.001	210 (94.6%)	211 (95.0%)	1
1	18 (3.6%)	38 (8.9%)		12 (5.4%)	11 (5.0%)	
Complication(DM/HT)						
Absence	470 (92.7%)	368 (86.4%)	0.002	199 (89.6%)	199 (89.6%)	1
Presence	37 (7.3%)	58 (13.6%)		23 (10.4%)	23 (10.4%)	
Hepatitis						
Non-viral	30 (5.9%)	32 (7.5%)	0.622	14 (6.3%)	21 (9.5%)	0.415
HBV	472 (93.1%)	390 (91.5%)		206 (92.8%)	198 (89.2%)	
HCV	5 (1.0%)	4 (0.9%)		2 (0.9%)	3 (1.4%)	
Cirrhosis						
No	0 (0%)	26 (6.1%)	<0.001	0 (0%)	1 (0.5%)	1
Yes	507 (100%)	400 (93.9%)		222 (100%)	221 (99.5%)	
Laboratory tests						
ALB, g/L	38.43±5.50	39.29±4.39	0.009	39.53±5.24	39.59±4.41	0.897
ALT, U/L	73.74±138.88	60.87±47.14	0.051	69.38±95.25	61.79±51.16	0.296
AST, U/L	110.71±168.95	104.10±88.28	0.445	69.38±95.25	61.79±51.16	0.296
TBIL, μmol/L	20.91±27.44	19.04±13.02	0.173	17.59±11.03	19.92±16.15	0.076
PLT, 10^9/L	89.05±56.50	257.87±126.12	0.000	88.40±46.58	251.34±105.62	0.000
AFP, ng/mL	28619.75±120,587.91	34,110.22 ±50,359.67	0.393	18,998.83 ±79,102.96	27,679.10 ±44,491.13	0.169
Child-Pugh class						
A	485 (95.7%)	414 (97.2%)	0.289	216 (97.3%)	217 (97.7%)	1
B	22 (4.3%)	12 (2.8%)		6 (2.7%)	5 (2.3%)	
Maximum tumor size, cm						
≤5	11 (2.2%)	5 (1.2%)	<0.001	6 (2.7%)	5 (2.3%)	0.75
5~10	151 (29.8%)	79 (18.5%)		57 (25.7%)	51 (23.0%)	
>10	345 (68.0%)	342 (80.3%)		159 (71.6%)	166 (74.8%)	

(*Continued*)

Table 1 (Continued).

Characteristic	Before PSM			After PSM		
	TACE (N=507)	HAIC (N=426)	P-value	TACE (N=222)	HAIC (N=222)	P-value
Number of HCC foci						
≤5	244 (48.1%)	168 (39.4%)	0.0094	89 (40.1%)	94 (42.3%)	0.7
>5	263 (51.9%)	258 (60.6%)		133 (59.9%)	128 (57.7%)	
Microvascular invasion						
Absence	218 (43.0%)	162 (38.0%)	0.141	140 (63.1%)	139 (62.6%)	1
Presence	289 (57.0%)	264 (62.0%)		82 (36.9%)	83 (37.4%)	
Portal vein tumor thrombosis						
Absence	218 (43.0%)	172 (40.4%)	<0.001	140 (63.1%)	139 (62.6%)	0.854
Vp1	0 (0%)	3 (0.7%)		0 (0%)	1 (0.5%)	
Vp2	1 (0.2%)	58 (13.6%)		1 (0.5%)	1 (0.5%)	
Vp3	2 (0.4%)	97 (22.8%)		2 (0.9%)	1 (0.5%)	
Vp4	286 (56.4%)	96 (22.5%)		79 (35.6%)	80 (36.0%)	
HVTT						
Absence	502 (99.0%)	356 (83.6%)	<0.001	219 (98.6%)	218 (98.2%)	0.801
I	2 (0.4%)	41 (9.6%)		2 (0.9%)	2 (0.9%)	
II	2 (0.4%)	7 (1.6%)		1 (0.5%)	1 (0.5%)	
III	1 (0.2%)	22 (5.2%)		0 (0%)	1 (0.5%)	
BCLC stages						
A	81 (16.0%)	41 (9.6%)	0.009	36 (16.2%)	40 (18.0%)	0.799
B	79 (15.6%)	60 (14.1%)		56 (25.2%)	51 (23.0%)	
C	347 (68.4%)	325 (76.3%)		130 (58.6%)	131 (59.0%)	
Extrahepatic spread						
Absence	353 (69.6%)	249 (58.5%)	<0.001	148 (66.7%)	146 (65.8%)	0.92
Presence	154 (30.4%)	177 (41.5%)		74 (33.3%)	76 (34.2%)	

Notes: Data are number of patients; data in parentheses are percentage unless otherwise indicated. Data in bracket was percent of patients. The quantitative data with mean± standard deviation or median with interquartile range (IQR) were compared by the Kruskal–Wallis test. The qualitative data in two groups were compared by using the Chi square test. P value < 0.05 suggest statistically significant differences. The variables matched included age.

Abbreviations: HCC, hepatocellular carcinoma; HAIC, hepatic arterial infusion chemotherapy; TACE, transcatheter arterial chemoembolization; PSM, propensity score match; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis type B viral; HCV, hepatitis type C viral; DM, diabetes mellitus; HT, hypertension; HVTT, hepatic vein tumor thrombosis; BCLC, Barcelona Clinic Liver Cancer.

Safety

The incidence of treatment-related AEs in the two groups is shown in Table 4. There were no treatment-related deaths in either group. The incidence of all grades of AEs in the TACE and HAIC groups was 95.5% (212/222) and 85.6% (190/222), respectively, and the difference between the two groups was statistically significant (*P*, 0.000). The AEs of any grade (>10%) are shown in the Supplementary Information E1.4. The incidence of grade 3 or 4 AEs was significantly lower in the HAIC group than in the TACE group (8.1% and 23.9%, *P*<0.001). The incidence of grade 3 or 4 AEs was greater than 10% in the TACE group, and the AEs included elevated ALT (67.6%), elevated AST (31.5%), and abdominal pain (13.1%). No grade 3 or 4 AEs occurred in more than 10% of the HAIC group.

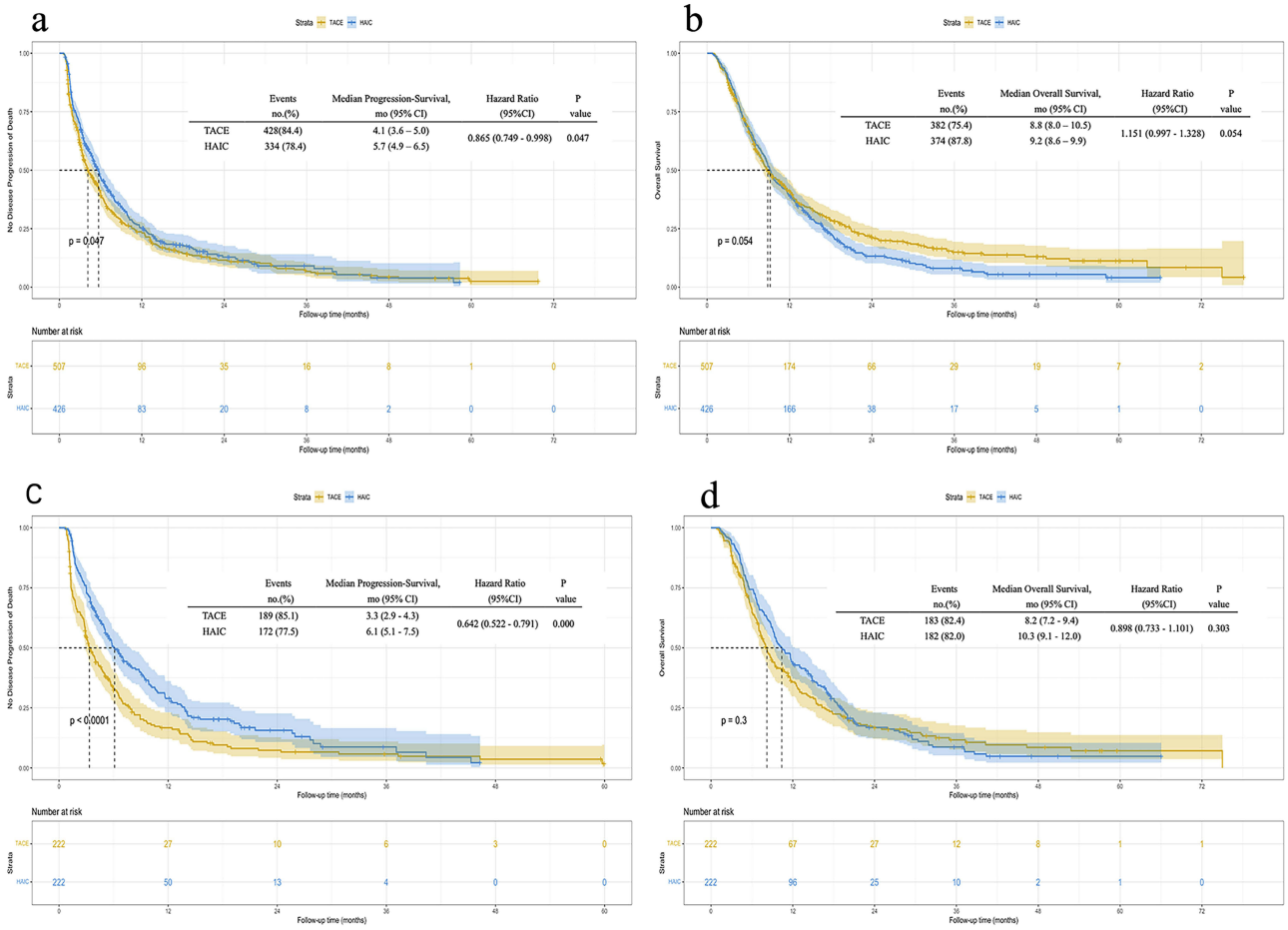

Figure 2 Comparison of survival between patients who received HAIC and TACE. Kaplan–Meier curves for the progression-free survival(PFS) and overall survival(OS) before and after propensity score matching (PSM).PFS before PSM (**a**), OS before PSM (**b**); PFS after PSM (**c**), OS after PSM (**d**).
Abbreviations: HAIC, hepatic arterial infusion chemotherapy; TACE, transarterial chemoembolization.

Discussion

This multicenter, retrospective, matched cohort-based study demonstrated that HAIC is feasible and safe in the treatment of HCC patients. In this study, HAIC significantly improved PFS and ORR in hHCC compared with TACE. Compared

Table 2 Summary of Best Overall Response Before and After PSM

Best Overall Response n(%)	Before PSM			After PSM		
	TACE (n=222)	HAIC (n=222)	P-value	TACE (n=507)	HAIC (n=426)	P-value
ORR	26 (11.7)	55 (24.8)	0.000	82 (16.2)	89 (20.9)	0.064
DCR	128 (57.7)	186 (83.8)	0.000	309 (60.9)	335 (78.6)	0.000
CSR	18 (8.1)	33 (14.9)	0.026	45 (8.9)	66 (15.5)	0.002
CR	1 (0.5)	2 (0.9)		3 (0.6)	2 (0.5)	
PR	25 (11.3)	53 (23.9)		79 (15.6)	87 (20.4)	
SD	102 (45.9)	131 (59.0)		227 (44.8)	246 (57.7)	
PD	94 (42.8)	36 (16.2)		198 (39.1)	91 (21.4)	

Notes: Data are number of patients; data in parentheses are percentage unless otherwise indicated and data in bracket was percent of patients. P value < 0.05 suggest statistically significant differences.
Abbreviations: PSM, propensity score match; ORR, objective response rate; DCR, Disease control rate; CSR, conversion surgery rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 3 Univariate and Multivariate Analysis of Risk Factors for Progression-Free Survival and Overall Survival After Matching

	Univariable Analysis		Multivariable Analysis	
	Hazard Ratio (95% CI)	**p-value**	**Hazard Ratio (95% CI)**	**P-value**
PFS analyses				
Age (≤65 vs >65)	0.64 (0.47–0.87)	0.004	0.73 (0.53–1.00)	0.052
Sex (Female vs Male)	1.05 (0.73–1.51)	0.797		
Hepatitis (Absence vs Presence)	1.14 (0.82–1.60)	0.439		
ECOG (0 vs 1)	0.38 (0.22–0.66)	0.001	0.48 (0.27–0.85)	0.011
Child-Pugh (A vs B)	1.00 (0.51–1.94)	0.994		
BCLC stage (A vs B vs C)	1.28 (1.11–1.47)	0.001	1.13 (0.96–1.34)	0.141
Complication (Absence vs Presence)	0.60 (0.42–0.86)	0.006	0.77 (0.53–1.13)	0.179
Maximum tumor size-cm (≤5 vs 5~10 vs >10)	1.13 (0.91–1.40)	0.260		
HVTT/IVCTT (Absence vs I–III)	0.72 (0.32–1.61)	0.417		
MVI (Absence vs Presence)	1.13 (0.91–1.40)	0.280		
Number of HCC foci (≤5 vs >5)	1.22 (0.98–1.51)	0.070		
PVTT (Absence vs Vp1-Vp3 vs Vp4)	1.03 (0.98–1.09)	0.272		
Extrahepatic spread (Absence vs Presence)	1.49 (1.20–1.86)	<0.001	1.20 (0.93–1.56)	0.166
Treatment (TACE vs HAIC)	0.64 (0.52–0.79)	<0.001	0.61 (0.49–0.75)	<0.001
OS analyses				
Age (≤65 vs >65)	0.628 (0.463–0.851)	0.003	0.75 (0.55–1.03)	0.073
Sex (Female vs Male)	1.07 (0.75–1.52)	0.711		
Hepatitis (Absence vs Presence)	1.15 (0.81–1.64)	0.426		
ECOG (0 vs 1)	0.75 (0.47–1.19)	0.218		
Child-Pugh (A vs B)	1.67 (0.89–3.14)	0.112		
BCLC stages (A vs B vs C)	1.33 (1.16–1.53)	<0.001	1.00 (0.78–1.28)	0.997
Complication (Absence vs Presence)	0.56 (0.39–0.81)	0.002	0.63 (0.43–0.92)	0.016
Maximum tumor size-cm (≤5 vs 5~10 vs >10)	1.16 (0.95–1.42)	0.152		
HVTT/IVCTT (Absence vs I–III)	0.67 (0.38–1.15)	0.145		
MVI (Absence vs Presence)	1.41 (1.15–1.74)	0.001	1.02 (0.28–3.71)	0.975
Number of HCC foci (≤5 vs >5)	1.39 (1.13–1.72)	0.002	1.25 (0.99–1.58)	0.061
PVTT (Absence vs Vp1-Vp3 vs Vp4)	1.09 (1.04–1.15)	0.001	1.08 (0.78–1.49)	0.661
Extrahepatic spread (Absence vs Presence)	1.41 (1.14–1.74)	0.002	1.31 (0.97–1.78)	0.08
Treatment (TACE vs HAIC)	0.90 (0.73–1.10)	0.3		

Note: The multivariable analysis includes the variables with P-value ≤0.1 from the univariable analysis.

Abbreviations: CI, confidence intervals; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; HVTT, hepatic vein Thrombosis; IVCTT, inferior vena cava tumor thrombus; MVI, microvascular invasion; PVTT, portal vein tumor thrombosis; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy.

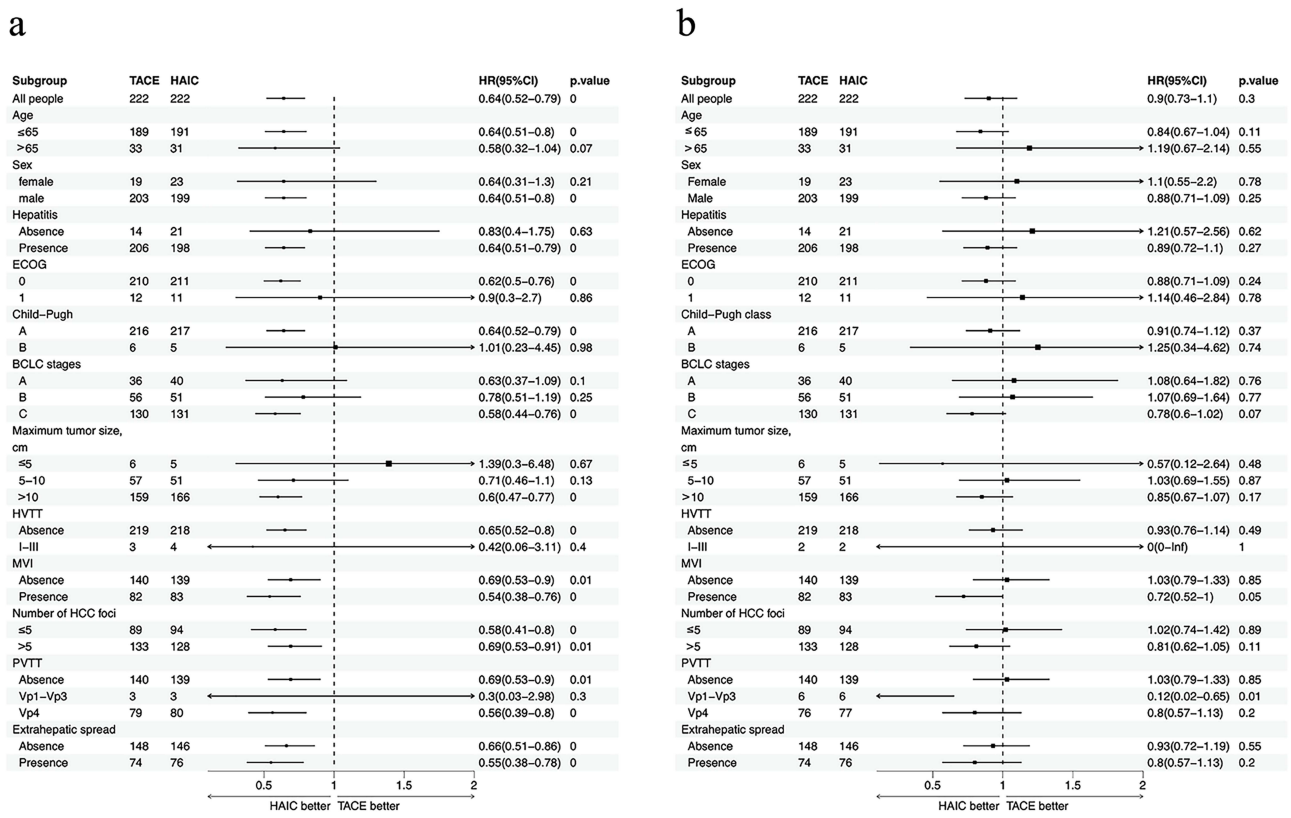

Figure 3 Forest plot showing the subgroup analysis of progression-free survival (**a**) and overall survival (**b**).
Abbreviations: HCC, hepatocellular carcinoma; HAIC, hepatic arterial infusion chemotherapy; TACE, transarterial chemoembolization; HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; HVTT, hepatic vein thrombosis; MVI, microvascular invasion; PVTT, portal vein tumor thrombosis.

with the IMbrave150 study, we enrolled a larger number of patients in the high-risk group (444 vs 101) and targeted this group for comparison of treatment modalities instead of using a post-hoc analyses, and this group targeting resulted in more reliable results, a longer median PFS (6.1 [95% CI 5.1–7.5] vs 3.3 [95% CI 2.9–4.3] months), and a longer median OS (10.3 [95% CI 9.1–12.0] vs 7.6 [95% CI 6.6–12.8] months). Among the subgroup analyses, tumor diameter greater than 10 cm and Vp4 staging were shown to have significant PFS benefits, and PVTT Vp1-3 had significant OS benefits.

Table 4 Treatment-Related Adverse Events

Event, n (%)	TACE(n, 222)			HAIC (n, 222)			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 TRAE	212(95.5)	208(93.7)	53(23.9)	190(85.6)	184(82.9)	18(8.1)	0.000	0.000	<0.001
Blood/bone marrow suppression									
Leukopenia	9(4.1)	9(4.1)	0(0)	44(19.8)	33(14.9)	22(9.9)	<0.001	<0.001	<0.001
Neutropenia	5(2.3)	7(3.2)	2(0.9)	53(23.9)	33(14.9)	13(5.9)	0.000	<0.001	0.004
Reduced hemoglobin level	82(36.9)	87(39.2)	2(0.9)	24(10.8)	20(9.0)	4(1.8)	0.000	0.000	0.411
Thrombocytopenia	31(14.0)	37(16.7)	5(2.3)	55(24.8)	46(20.7)	11(5.0)	0.004	0.273	0.127
Constitutional symptom									
Fever	82(36.9)	80(36.0)	3(1.4)	20(9.0)	20(9.0)	0(0)	0.000	0.000	0.082

(*Continued*)

Table 4 (Continued).

Event, n (%)	TACE(n, 222)			HAIC (n, 222)			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
Hepatic function									
Elevated ALT level	129(58.1)	150(67.6)	31(14.0)	90(40.5)	90(40.5)	2(0.9)	<0.001	<0.001	<0.001
Elevated AST level	167(75.2)	129(58.1)	70(31.5)	125(56.3)	143(64.4)	7(3.2)	<0.001	0.173	0.000
Elevated total bilirubin level	65(29.3)	71(32.0)	20(9.0)	24(10.8)	24(10.8)	2(0.9)	<0.001	<0.001	<0.001
Hypoalbuminemia	80(36.0)	82(36.9)	2(0.9)	68(30.6)	59(26.6)	7(3.2)	0.227	0.019	0.092
Gastrointestinal events									
Abdominal pain	95(42.8)	114(51.4)	29(13.1)	114(51.4)	114(51.4)	0(0)	0.071	>0.999	<0.001
Constipation	54(24.3)	54(24.3)	2(0.9)	66(29.7)	66(29.7)	0(0)	0.200	0.200	0.156
Diarrhea	13(5.9)	13(5.9)	2(0.9)	42(18.9)	42(18.9)	0(0)	<0.001	<0.001	0.156
Nausea	105(47.3)	105(47.3)	2(0.9)	46(20.7)	46(20.7)	0(0)	<0.001	<0.001	0.156
Vomiting	29(13.1)	31(14.0)	3(1.4)	20(9.0)	18(8.1)	15(6.8)	0.173	0.049	0.004

Notes: Data are number of patients; data in parentheses are percentage unless otherwise indicated. Data in bracket was percent of patients. The qualitative data in two groups were compared by using the Chi square test. P value < 0.001 suggest statistically significant differences.
Abbreviations: TRAE, treatment-related adverse events; HAIC, hepatic arterial infusion chemotherapy; TACE, transarterial chemoembolization.

In this study, HAIC was not significantly different from TACE, although the median OS was prolonged in the HAIC group (10.3 [95% CI 9.1–12.0] vs 7.6 [95% CI 6.6–12.8] months). HAIC provided a significant clinical benefit in terms of PFS, regardless of the presence or absence of microvascular invasion, extrahepatic metastases, and tumor number, after combining the results of the subgroup analysis with the results of the following groups: age≤65 years, male, absence of hepatitis, ECOG score 0, Child–Pugh A, BCLC grade C, no complications, tumor diameter greater than 10 centimeters, no hepatic vein tumor thrombus, PVTT Vp4 and no PVTT. It is possible to suggest that we should be more careful about the selection of patient groups and that treating HAIC in patients within hHCC may be more suitable for younger patients with better liver function as well as physical strength. Additionally, considering HAIC as a local treatment, the present study has shown benefits in ORR (24.8% vs 11.7%, *P*=0.000) and DCR (83.8% vs 57.7%, *P*=0.000), and in a multicenter retrospective study comparing HAIC plus Lenvatinib and tislelizumab with or without TACE (THLP vs HLP) for the treatment of HCC populations with combined PVTT and high tumor load, the median OS and PFS for the entire cohort were 12.5 months (95% CI, 10.9–14.8) and 5.0 months (95% CI, 4.2–5.4), respectively.[19] A subsequent combination of systemic therapy is needed to achieve better clinical benefit and further prolong OS.

The advantage of HAIC over TACE is that HAIC is a local continuous drug delivery strategy, unlike TACE, which requires embolization of the hepatic artery to avoid further deterioration of hepatic function. PVTT itself can reduce intrahepatic blood flow and cause portal hypertension, which leads to hepatic impairment, and if the hepatic artery is further embolized at this time, it is difficult to not further deteriorate hepatic function, which can delay or even interrupt systemic administration of therapy after localized treatment. A meta-analysis of patients with HCC treated with HAIC versus sorafenib in combination with PVTT[20] showed that HAIC was more effective in patients with PVTT Vp 3–4 than in patients with PVTT Vp 2–3 (HR for OS: 0.42 vs 0.56, HR for PFS: 0.35 vs 0.59), and a further meta-analysis based on the subgroups of tumor remission showed that the incidence of PD was superior in patients with HCC involving the main trunk of the portal vein (Vp 3–4) compared to patients with portal vein terminal thrombus (Vp 2–4). In this study, subgroup analyses showed that a significant OS benefit was obtained in patients with combined PVTT Vp 1–3. A significant PFS benefit was obtained in Vp4. Although TACE is a common therapeutic tool, the efficacy of TACE depends largely on tumor size during the current treatment or the treatment of high tumor load. The rate of complete

tumor remission was significantly lower in tumors larger than 5 cm in diameter. In this study, the subgroup analysis showed that patients with tumor diameters greater than 10 cm had a PFS benefit, while no significant benefit was observed in terms of OS. HCC patients with bile duct invasion have a poor prognosis and are prone to comorbid PVTT. There are few studies on the treatment options for this group of HCC patients. The basis for determining bile duct invasion in the clinic remains distal biliary dilatation, and postoperative pathology is still the gold standard for determining bile duct invasion. The survival outcome of patients undergoing TACE has been found to be superior to that of patients undergoing conservative treatment or systemic chemotherapy. It is unfortunate that in the present study, the patients with bile duct invasion were not clearly counted due to the use of clinical limitations of the retrospective collection of case data.

In terms of safety, there were some differences in the frequency and severity of AEs between the TACE and HAIC groups. The TACE group had a higher incidence of total AEs and grade 3–4 AEs than the HAIC group. The most common grade 3–4 AEs in the TACE group were elevated ALT (67.6%), elevated AST (31.5%), and abdominal pain (13.1%). This may be related to embolization-related liver injury and ischemic necrosis in HCCa. No grade 3 or 4 AEs occurred in more than 10% of the HAIC group. Leukopenia (19.8%), neutropenia (23.9%), decreased hemoglobin (10.8%), decreased platelets (24.8%), elevated aspartate aminotransferase (56.3%), nausea (20.7%), elevated alanine aminotransferase (40.5%), elevated total bilirubin (10.8%), constipation (29.7%), and diarrhea (18.9%) were more prevalent, possibly due to chemotherapy-induced bone marrow suppression and liver injury. The higher incidence of abdominal pain, nausea, and vomiting may be caused by chemotherapy, especially drug diversion to the gastrointestinal tract or gallbladder, so sometimes we perform gastroduodenal artery embolization during HAIC to reduce drug diversion. Meanwhile, some data details were missing due to the limitations of the retrospective study. Nevertheless, the results of the study showed that the safety of HAIC for hHCC is acceptable and similar to the results of existing studies.[21,22]

There are some limitations of this study. This is a retrospective study, which inevitably introduces selection bias as well as the effect of confounding factors, so we used PSM to eliminate between-group variability. Second, our study population was heterogeneous, including patients with different disease stages and different clinical presentations. This heterogeneity may affect the interpretation of our results and their applicability because we included hHCC in this study, and this heterogeneity is difficult to avoid, which is why it is difficult to carry out prospective cohort studies in this group. Third, It is conceivable that the limited sample size in this study may have influenced the absence of significant OS outcomes. Therefore, when interpreting this aspect of the results, caution is paramount. In the future, we aim to broaden the participant pool to enable a more comprehensive comparison of the efficacy and safety of the two topical treatments. Finally, in this study only the feasibility and safety of localized treatments were compared, which resulted in a limited benefit, and therefore, we need to follow up with further explorations to validate the combination of systemic therapy with HAIC. Therefore, we need to further explore and validate the efficacy and safety of HAIC combined with systemic therapy.

In summary, this study confirms the effectiveness and safety of HAIC in the treatment of hHCC, and the benefit of HAIC compared with TACE for patients' liver function also creates favorable conditions for us to add systemic therapy in the follow-up. In the future, we are carrying out real-world studies of HAIC combined with systemic therapy for hHCC, which will bring greater benefits to patients.

Abbreviations

HCC, hepatocellular carcinoma; HAIC, hepatic arterial infusion chemotherapy; TACE, transcatheter arterial chemoembolization; hHCC, high-risk hepatocellular carcinoma; PSM, propensity score match; OS, Overall survival; PFS, progression-free survival; ORR, Objective response rate; CSR, conversion surgery rate; AEs, adverse events.

Statistics and Biometry

No complex statistical methods were necessary for this paper.

Study Subjects or Cohorts Overlap

There are no study subjects or cohorts have been previously reported.

Guarantor

The scientific guarantor of this publication is Dong Yan.

Ethics

This retrospective multicenter study obtained institutional review board approval from all participating hospitals (Beijing Luhe Hospital Affiliated to Capital Medical University, Sun Yat-sen University Cancer Center, The First Affiliated Hospital of Sun Yat-sen University, The Third Affiliated Hospital of Sun Yat-sen University, Cancer Hospital Chinese Academy of Medical Sciences, Guangdong Provincial People's Hospital) and all enrolled patients signed an informed consent form. All participants in this study promised to maintain the confidentiality of all patient data and strictly abide by the Declaration of Helsinki.

Acknowledgments

We would like to thank all the participants who participated in this study.

Funding

This study has received funding by the capital health research and development of special. (2022-2-7083); R&D Program of Beijing Municipal Education Commission (KM202010025005); Beijing Municipal Natural Science Foundation 7222100.

Disclosure

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

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