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Original Article

Effect of Huaier Granules combined with transarterial chemoembolization on recurrence and survival in postoperative hepatocellular carcinoma patients with microvascular invasion

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Abstract: Objective: To evaluate whether Huaier Granules combined with transcatheter arterial chemoembolization (TACE) reduces recurrence and improves survival in patients with microvascular invasion (MVI)-positive primary hepatocellular carcinoma (HCC) after resection. Methods: A single-center retrospective study enrolled 266 patients (2019-2021), who were divided into the Huaier Granules + TACE group (Observation Group) (n=137) and the TACE alone group (Control Group) (n=129). Key outcomes included recurrence-free survival (RFS), overall survival (OS), objective response rate (ORR), liver function, adverse events (AEs), and health-related quality of life (HRQoL) assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Hepatocellular Carcinoma 18-question module. Survival was analyzed using the Kaplan-Meier method; Cox regression and receiver operating characteristic (ROC) analysis were employed to explore prognostic factors and evaluate discrimination. Results: Compared with TACE alone, the combination group had a higher ORR (55.47% vs 38.76%, P<0.005), lower 1-/2-/3-year recurrence rates (16.79%/44.53%/78.10% vs 26.36%/53.48%/89.15%, P<0.05), and longer RFS and OS (both P<0.05). The combination group exhibited more significant improvements in alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBil), and albumin (ALB) (all P<0.05), with a comparable AE rate (P>0.05) and better 3-month HRQoL (all P<0.05). Multivariable analysis identified Tumor-Node-Metastasis (TNM) stage, post-treatment AST, and treatment modality as independent predictors of 3-year mortality, with modest area under the curve values (0.572-0.699). Conclusion: Huaier Granules combined with TACE was associated with reduced recurrence, prolonged survival, favorable safety, and better short-term HRQoL in this cohort. These findings require cautious interpretation and prospective validation due to the study's limitations.

Keywords: Huaier Granules, transcatheter arterial chemoembolization, primary hepatocellular carcinoma, microvascular invasion, survival analysis

Introduction

Primary liver cancer is the sixth most commonly diagnosed cancer worldwide and the third leading cause of cancer death, and hepatocellular carcinoma (HCC) accounts for the great majority of cases [1]. For patients with early-stage HCC, surgical resection remains a cornerstone treatment, yet postoperative recurrence is frequent and largely determines long-term outcomes. In some resected cohorts, cumulative recurrence has reached 60-80% within several years, underscoring the need for effective adjuvant strategies [2]. Among pathological features, microvascular invasion (MVI) - defined as microscopic tumor thrombi within small intrahepatic vessels - is a consistent predictor of early relapse and poor survival [3]. In clinical practice, MVI is commonly stratified into M1 (≤5 foci within or adjacent to the tumor margin) and M2 (>5 foci or any foci distant from the margin) based on the number and location of foci [4-7]. The risk of recurrence rises sharply in the presence of MVI. For example, Yamashita et al. reported a 1-year recurrence rate of 23.3% in patients with MVI versus 7.5% in those without

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[5, 6], and lower 1-, 3-, and 5-year overall survival rates have been observed in MVI-positive patients after liver transplantation.

TACE delivers chemotherapeutic agents and embolic materials into tumor-feeding arteries, aiming to induce ischemic necrosis while concentrating cytotoxic exposure. TACE is widely used in intermediate-stage HCC and as adjuvant or post-recurrence therapy after resection. However, its durability is limited by neovascularization, collateral vessel formation, and the potential for cumulative liver injury with repeated sessions. High post-TACE recurrence rates remain a practical challenge, and optimizing combination therapies to enhance disease control without excessive toxicity has become a clinical focus [7-10].

Huaier Granule (Trametes robiniophila murr.), a commonly used traditional Chinese medicine preparation for the adjuvant treatment of liver cancer, offers a novel approach to addressing the limitations of TACE efficacy when used in combination therapy. Clinical studies have confirmed that Huaier Granule exerts a synergistic anti-cancer effect by regulating the tumor microenvironment and enhancing anti-tumor immune responses. A prospective cohort study showed that Huaier Granules combined with targeted therapy plus immunotherapy significantly prolonged the median progression-free survival (mPFS: 8.9 months vs. 5 months) of patients with unresectable HCC, as well as reduced the risk of disease progression by 47%, and yielded more significant benefits in patients with vascular invasion [10, 11]. However, this study had a single-center design, small sample size (n=126), and lacked a blind control, leading to certain selection bias and a moderate level of evidence. Another cohort study indicated that Huaier Granules could prevent recurrence after local treatment of early-stage HCC, but it only had a follow-up period of 18 months, and it failed to conduct explicit stratified analysis on the efficacy difference in MVI-positive populations, plus it lacked systematic evaluation of adverse reactions, resulting in insufficient evidence completeness [11]. It should be objectively noted that high-quality evidence on the combined application of Huaier Granules and TACE in post-operative patients with MVI-positive HCC is currently scarce. Most existing studies have design flaws or population limitations, which provides a clear research gap for this study to explore the efficacy and safety of this combined strategy.

Against this backdrop, we examined whether adding Huaier Granules to TACE after curative resection could mitigate early relapse and improve survival in patients with HCC and MVI. We focused on outcomes that matter clinically - recurrence-free survival, overall survival, liver function, quality of life and safety - while we explored which patient or treatment factors shape prognosis. The goal of this research is to provide pragmatic evidence to inform post-surgical management in this high-risk group.

Methods and materials

Case selection

This retrospective study enrolled 266 patients with primary HCC and MVI from Baoji Traditional Chinese Medicine Hospital between February 2019 and April 2021. Based on the different treatment approaches documented in their medical records, patients were divided into the observation group (137 cases) receiving Huaier Granules combined with TACE and the control group (129 cases) receiving TACE alone. This study was conducted after approval by the Ethics Committee of Baoji Traditional Chinese Medicine Hospital, in compliance with ethical standards for medical research involving human subjects. Inclusion criteria: ① Met the diagnostic criteria specified in the “Guidelines for Diagnosis and Treatment of Primary Liver Cancer” [12, 13]; ② age >18 years; ③ TNM stage II-IV HCC; ④ Estimated survival ≥12 weeks; ⑤ No prior chemotherapy, immunotherapy, targeted therapy, or other systemic treatments before enrollment or during the study; ⑥ Complete clinical medical records available, with clear follow-up outcomes (e.g., survival status, recurrence, metastasis, or death) documented during the study period.

Exclusion criteria: ① Presence of other malignant tumors; ② Cognitive impairment or mental disorders; ③ Pregnant or lactating women; ④ Severe hepatic or renal insufficiency.

Treatment methods

The Seldinger technique was used for femoral artery puncture, followed by catheterization into the tumor-feeding artery for TACE. A triple chemotherapy regimen consisting of epirubicin, cisplatin, and fluorouracil was adopted, with doses calculated based on body surface area (epirubicin 50 mg/m^2, cisplatin 60 mg/m^2, fluorouracil 500 mg/m^2). Ultra-liquefied lipiodol served as the basic embolic agent (dosage

5-15 mL per session, adjusted according to tumor volume), combined with 100-300 μm gelatin sponge particles. For patients with rich tumor blood supply or complicated with arteriovenous fistulas, 300-500 μm polyvinyl alcohol (PVA) particles were added to enhance the embolization effect.

The initial treatment interval was 4-6 weeks. Efficacy was evaluated by imaging after the first treatment. Patients with residual lesions underwent repeated TACE at 4-week intervals until the best therapeutic effect was achieved or the patient could not tolerate further treatment. Both groups received 1-3 TACE sessions, with an average of 1.7-1.8 sessions. The regimen was strictly adjusted based on the principle of individualization: patients with Child-Pugh class A received standard doses; those with class B had chemotherapy doses reduced by 50% and embolic agent doses reduced by 30%; patients with class C received treatment only after liver function improvement. For tumors with a maximum diameter ≤5 cm, lipiodol was the main embolic agent; for tumors >5 cm or multiple nodules, the dosage of PVA particles was increased and segmental embolization was adopted. In case of grade 3 or higher adverse reactions, treatment was delayed to 6-8 weeks or further dose reduction was implemented.

The observation group started taking Huaier Granules (Qidong Gaitianli Pharmaceutical Co., Ltd., National Medicine Approval Number Z20000183) 3 days after embolization, at a dose of 20 g three times daily, continuously for at least 3 months. If intolerable adverse reactions occurred, the dosage could be temporarily reduced or discontinued. Both groups routinely received polyene phosphatidylcholine for liver protection, pantoprazole for acid suppression, and anti-inflammatory and supportive treatments after surgery to ensure treatment safety.

Observation indicators

Primary observation indicators: (1) Treatment efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. The observation group began follow-up, after initiating Huaier Granules, via phone calls, hospital readmissions, and outpatient visits, with recurrence and survival status collected within 3 years after the first chemotherapy session, and a follow-up frequency of once monthly. The control group started follow-up after the first TACE session. Clinical responses were classified into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Objective response rate (ORR) was defined as the sum of CR and PR. PR was defined as a ≥30% reduction in tumor lesion volume on imaging compared with pre-treatment. SD was defined as a tumor volume reduction of <30% or an increase of ≤25%. PD was defined as a tumor volume increase of >25% or the appearance of new lesions [13, 14]. (2) All patients were followed up for 3 years. Recurrence-free survival (RFS), overall survival (OS) within 3 years were recorded for both groups. Recurrence rates from year 1 to year 3 were compared between groups.

Secondary observation indicators: (1) Treatment-related adverse events were recorded in both groups, including gastrointestinal reactions, fever, hand-foot syndrome, and myelosuppression. (2) Liver function indicators (alanine aminotransferase (ALT), aspartate aminotransferase (AST) albumin [Alb], and total bilirubin [TBil]) were measured using a Beckman Coulter automated biochemical analyzer (Model: AU680, USA). Changes in liver function indicators before and after treatment were compared between groups. (3) Health-related quality of life (HRQoL) at 1 month and 3 months post-treatment was evaluated using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Hepatocellular Carcinoma 18-question module (EORTC QLQ-HCC18). The Chinese version of this scale contains 18 items covering 8 domains: fatigue, body image, jaundice, nutrition, pain, fever, abdominal distension, and sexual activity. Each domain or item was converted to a 0-100 score according to the scoring manual. The Cronbach's α coefficient of the scale was 0.830 [14, 15]. To integrate the total EORTC QLQ-HCC18 score, the QLQ-HCC18 index was used to define overall health-related quality of life (HRQoL). The QLQ-HCC18 index was calculated as (fatigue + body image + jaundice + nutrition + pain + fever + abdominal distension + sexual activity)/8. Higher scores indicate worse overall HRQoL [15]. (4) Independent factors affecting patient prognosis were analyzed by univariate and multivariate analyses. (5) ROC curves were used to test the prognostic predictive value of independent prognostic factors.

Statistical analysis

Statistical analysis was performed using SPSS 20.0 software (IBM Corporation). Measurement data were expressed as mean ± standard deviation (mean ± SD), and independent sample t-tests were used to compare means between groups. Count data were expressed as cases and percentages, and were analyzed using χ^2 tests. Ordinal data were analyzed using rank-sum tests, expressed as Z values. Kaplan-Meier (K-M) survival analysis was used to assess 3-year RFS and OS, with log-rank tests for comparison. A *P* value <0.05 was considered statistically significant.

Results

Comparison of baseline characteristics

There were no statistical differences in age, sex, smoking history, TNM stage, MVI classification, Karnofsky Performance Status (KPS) score, alpha-fetoprotein, AST/ALT ratio, total bilirubin, albumin, number of intrahepatic lesions, presence of extrahepatic metastasis, or portal vein tumor thrombus between groups (all P>0.05), as shown in **Table 1**.

Comparison of treatment efficacy

CT scans before and after treatment evaluated tumor treatment efficacy. Imaging results for the four efficacy grades are shown in **Figure 1**. Rank sum tests revealed significantly superior treatment efficacy in the observation group compared to the control group (P=0.010). The observation group achieved an ORR of 55.47% versus 38.76% in the control group, showing a significantly higher ORR in the observation group (P<0.005), as shown in **Table 2**.

Comparison of M2 distribution

Rank sum tests found significant differences in M2 distribution between the observation and control groups (P=0.028), as shown in **Table 3**. Among patients achieving ORR, the proportion of M2 patients was higher in the observation group (41.03%) compared to the control group (14.29%).

Comparison of 3-year OS and RFS

Statistics on 3-year survivors and recurrence-free survivors are shown in **Figure 2**. The control group had 36 survivors at 3 years (27.91%) and 14 recurrence-free survivors (10.85%), both lower than the observation group, which had 57 survivors (41.61%) and 30 recurrence-free survivors (21.90%). K-M curves demonstrated that both 3-year OS and RFS were significantly longer in the observation group than in the control group (P<0.001), as shown in **Figure 3**.

Comparison of 1- to 3-year recurrence and mortality rates

Results showed the control group had recurrence rates of 26.36% within 1 year, 53.48% within 2 years, and 89.15% within 3 years, all higher than the observation group's rates of 16.79%, 44.53%, and 78.10%, respectively (all P<0.05). Mortality rates from year 1 to year 3 were also significantly higher in the control group than in the observation group (all P< 0.05), as shown in **Table 4**.

Comparison of liver function indicator changes post-surgery

No statistical differences were found in pre-treatment AST, ALT, Alb, and TBil levels between the two groups (all P>0.05). After treatment, significant differences in AST, ALT, Alb, and TBil levels were observed between the groups (all P<0.001), as shown in **Table 5**.

Comparison of quality of life assessment post-surgery

At 1 month post-treatment, only pain and fever showed significant differences between groups (both P<0.05), with the control group experiencing more severe fever and pain distress than the observation group. At 3 months, all 8 domain scores showed significant differences (all P<0.05), with the control group experiencing more severe distress across all domains. For overall HRQoL, the observation group had superior health-related quality of life at both 1 month and 3 months post-treatment compared to the control group (all P<0.05), as shown in **Table 6**.

Comparison of adverse event occurrence

After treatment, adverse reactions in both the groups were predominantly mild grade 1-2 events, mainly including gastrointestinal reactions, fever, hand-foot syndrome, and myelosuppression. In the TACE alone group, there were 7 cases of gastrointestinal reactions

Table 1. Comparison of baseline characteristics (n (%))

Clinical Features	Observation Group (n=137)	Control Group (n=129)	χ^2	P
Age (years)			0.024	0.488
>60	82 (59.85)	76 (58.91)		
≤60	55 (40.15)	53 (41.09)		
Sex			0.292	0.351
Female	28 (20.44)	23 (17.83)		
Male	109 (79.56)	106 (82.17)		
TNM Stage			0.073	0.964
Stage II	72 (55.81)	75 (54.74)		
Stage III	47 (36.43)	52 (37.96)		
Stage IV	10 (7.75)	10 (7.30)		
MVI Classification			0.059	0.458
M1	98 (71.53)	94 (72.87)		
M2	39 (28.47)	35 (27.13)		
KPS Score			0.104	0.431
90 points	105 (76.60)	101 (78.29)		
70-80 points	32 (23.36)	28 (21.71)		
Extrahepatic Metastasis			0.03	0.545
No	123 (95.35)	130 (94.89)		
Yes	6 (4.65)	7 (5.11)		
Alpha-fetoprotein (μg/L)			0.182	0.383
<400	89 (64.96)	87 (67.44)		
≥400	48 (35.04)	42 (32.56)		
AST/ALT			0.312	0.355
<2	122 (89.05)	112 (86.82)		
≥2	15 (10.95)	17 (13.18)		
Total Bilirubin (μg/L)			0.048	0.461
<17	64 (46.72)	62 (48.06)		
≥17	73 (53.28)	67 (51.94)		
Albumin (g/L)			0.719	0.237
<36	47 (34.31)	38 (29.46)		
≥36	90 (65.69)	91 (70.54)		
Smoking History			0.162	0.401
Yes	27 (19.71)	28 (21.71)		
No	110 (18.98)	101 (78.29)		
Number of Intrahepatic Lesions			0.159	0.403
Solitary	26 (81.02)	27 (20.93)		
Multiple	111 (17.05)	102 (79.03)		
Portal Vein Tumor Thrombus			0.279	0.523
No	135 (98.54)	128 (99.22)		
Yes	2 (1.46)	1 (0.78)		

Note: TNM: Tumor Node Metastasis, MVI: Microvascular Invasion, KPS: Karnofsky Performance Status Scale, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase.

(5.43%), 3 cases of fever (2.33%), 5 cases of hand-foot syndrome (3.88%), and 4 cases of myelosuppression (3.10%), with a total adverse event rate of 14.73%. In the Huaier Granules combined with TACE group, there were 5 cases of gastrointestinal reactions (3.65%), 4 cases of fever (2.92%), 3 cases of hand-foot syndrome (2.19%), and 4 cases of myelosup-

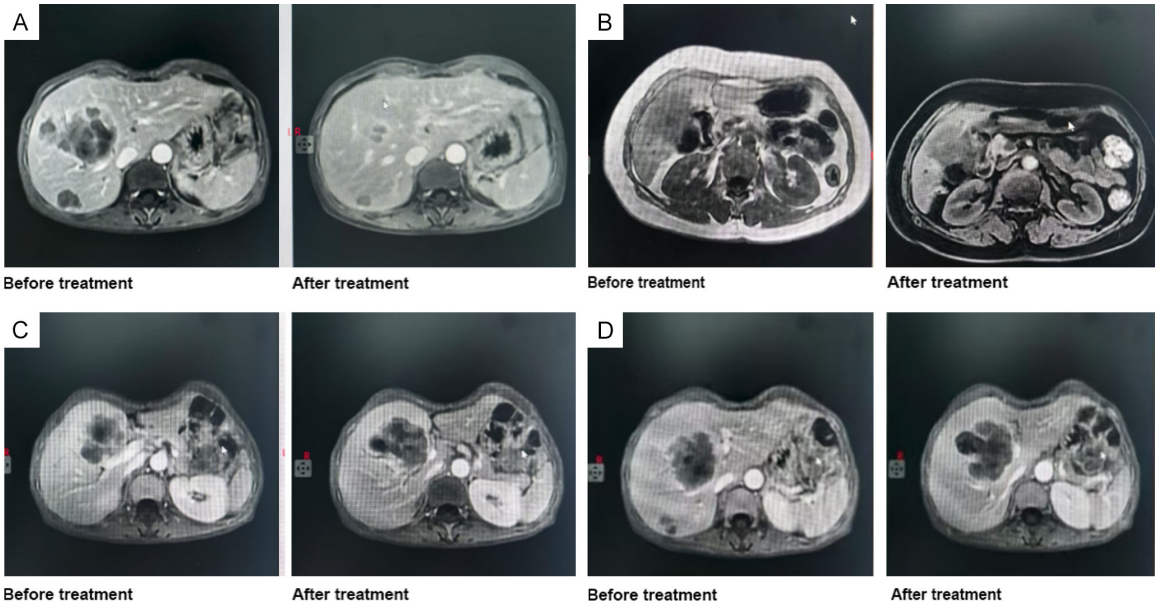


Figure 1. Comparison of imaging examinations before and after treatment. A. Complete response on imaging examination. B. Partial response on imaging examination. C. Stable disease on imaging examination. D. Progressive disease on imaging examination.

Table 2. Comparison of treatment efficacy between groups (n (%))

	CR	PR	SD	PD	ORR
Control Group (n=129)	1 (0.78)	49 (37.98)	53 (41.09)	26 (20.16)	50 (38.76)
Observation Group (n=137)	4 (2.92)	72 (52.55)	40 (29.20)	21 (15.33)	76 (55.47)
Z/χ^2				2.587	7.445
P				0.01	0.005

Note: CR: Complete Response, PR: Partial Response, SD: Stable Disease, PD: Progressive Disease, ORR: Objective Response Rate.

Table 3. Treatment efficacy in patients with MVI M2 classification (n (%))

	CR	PR	SD	PD	ORR
Control Group (n=35)	0 (0)	5 (14.29)	10 (28.57)	20 (57.14)	5 (14.29)
Observation Group (n=39)	1 (2.56)	15 (38.46)	14 (35.90)	9 (23.08)	16 (41.03)
Z/χ^2				1.463	6.489
P				0.028	0.01

Note: CR: Complete Response, PR: Partial Response, SD: Stable Disease, PD: Progressive Disease, ORR: Objective Response Rate.

pression (2.92%), with a total adverse event rate of 11.68%. All adverse events were relieved after routine symptomatic treatment and supportive nursing care, as shown in **Table 7**.

Univariate analysis of factors affecting 3-year prognosis

Among 266 patients, 173 survivors at 3 years were included in the survival group, and 93 deceased patients were included in the death group. Univariate analysis found that age, number of intrahepatic lesions, presence of extrahepatic metastasis, post-treatment ALT, Alb, and TBil were not associated with 3-year mortality (all P>0.05). However, TNM stage, smoking history, MVI classification, KPS score, treatment modality, and post-treatment AST may be influencing factors for 3-year mortality (all P<0.05), as shown in **Table 8**.

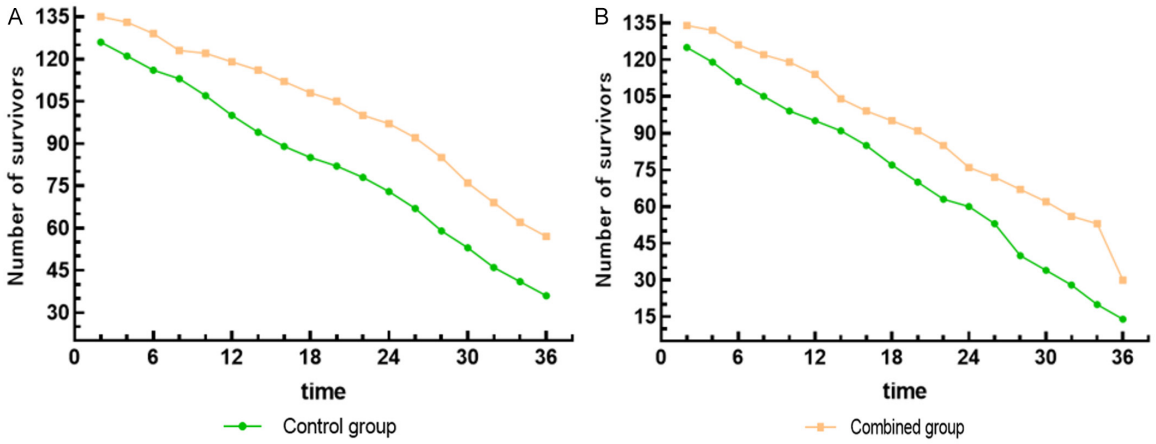
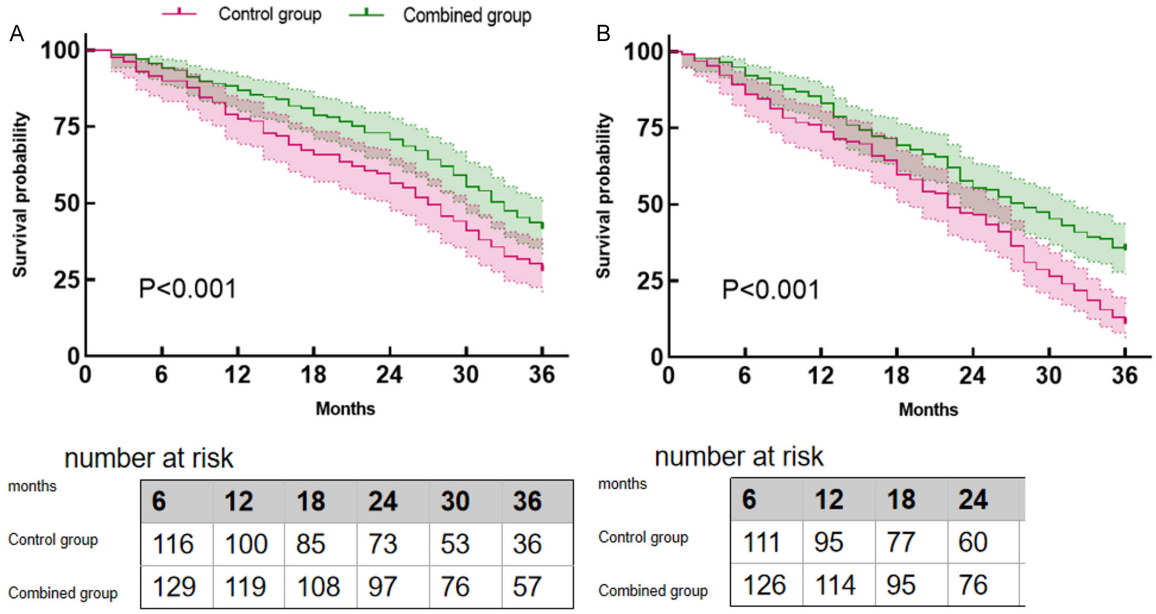


Figure 2. Comparison of 3-year survival numbers and recurrence-free survival numbers between groups. A. Number of surviving patients within 3 years. B. Number of recurrence-free surviving patients within 3 years.



number at risk

months	6	12	18	24	30	36
Control group	116	100	85	73	53	36
Combined group	129	119	108	97	76	57

number at risk

months	6	12	18	24
Control group	111	95	77	60
Combined group	126	114	95	76

Figure 3. Comparison of 3-year survival outcomes between groups. A. K-M curves for OS within 3 years. B. K-M curves for RFS within 3 years. Note: OS: Overall Survival, RFS: Recurrence-Free Survival, K-M: Kaplan-Meier.

Table 4. Comparison of recurrence rates between groups (n (%))

	1-Year Recurrence	2-Year Recurrence	3-Year Recurrence	1-Year Mortality	2-Year Mortality	3-Year Mortality
Control Group (n=129)	34 (26.36)	69 (53.48)	115 (89.15)	29 (22.48)	56 (43.41)	93 (72.09)
Observation Group (n=137)	23 (16.79)	61 (44.53)	107 (78.10)	18 (13.14)	40 (29.20)	80 (58.39)
χ^2	3.613	2.136	5.871	3.986	5.82	5.483
P	0.04	0.09	0.011	0.033	0.011	0.013

Multivariate analysis of factors affecting 3-year prognosis

Multivariate COX analysis revealed that MVI classification and smoking status were not independent factors affecting 3-year mortality (P>0.05). Advanced TNM stage (OR=1.507, 95% CI=1.033-2.199, P=0.033), higher post-treatment AST levels (OR=1.118, 95% CI= 1.014-1.294, P=0.036), and TACE alone treat-

Table 5. Comparison of liver function changes between groups

	AST (U/L)		ALT (U/L)		Alb (g/L)		TBil (μmol/L)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Observation Group (n=137)	51.14±7.77	28.31±5.92*	53.70±7.18	26.52±4.25*	35.36±3.20	37.76±3.29*	34.22±3.58	33.37±2.29*
Control Group (n=129)	51.77±7.25	35.28±6.73*	53.36±7.42	31.52±6.57*	35.41±3.12	34.85±3.28*	34.13±3.96	35.85±2.28*
t	-0.683	-8.981	0.38	-7.412	0.129	7.22	0.195	-8.846
P	0.495	<0.001	0.704	<0.001	0.898	<0.001	0.846	<0.001

Note: AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, Alb: Albumin, TBil: Total Bilirubin. *P<0.05 compared with pre-treatment in the same group.

Table 6. Evaluation of post-surgical health-related quality of life between groups

Time Point	Group	Domain Scores								
		Abdominal Distension	Body Image	Jaundice	Pain	Fever	Nutrition	Fatigue	Sexual Activity	QLQHCC18 Index
1 Month Post-treatment	Control Group (n=129)	35.21±18.04	27.41±17.58	26.61±15.33	28.98±18.20	13.08±9.22	28.70±18.34	35.71±19.34	30.55±17.38	28.28
	Observation Group (n=137)	33.76±17.32	27.36±17.03	25.11±15.38	24.07±18.85	10.09±9.14	26.38±17.22	33.96±19.68	28.91±16.94	26.21
	t	0.668	0.024	0.796	2.175	2.655	1.064	0.731	0.779	
	P	0.505	0.981	0.427	0.03	0.008	0.288	0.465	0.437	
3 Months Post-treatment	Control Group (n=124)	39.92±19.04	32.95±18.39	29.34±16.71	35.75±19.28	14.36±10.25	33.70±17.52	39.88±19.76	35.39±17.34	32.66
	Observation Group (n=135)	35.01±17.25	28.13±18.22	25.12±15.99	30.63±17.46	10.77±9.89	28.34±18.67	35.02±18.55	30.08±18.21	27.89
	t	2.177	2.117	2.076	2.233	2.863	2.377	2.036	2.398	
	P	0.030	0.035	0.039	0.026	0.005	0.018	0.043	0.017	

Table 7. Comparison of adverse events between groups (n (%))

Adverse Event	Group	Grade 1-2 (n, %)	Grade 3-4/Serious Adverse Events (SAE) (n, %)	Chi-square (χ^2)	*P* Value	Treatment Measures
Gastrointestinal reactions	Control Group (n=129)	7 (5.43)	1 (0.78)	0.188	0.432	Relieved after antiemetic symptomatic treatment.
	Observation Group (n=137)	5 (3.65)	1 (0.73)			Relieved after antiemetic symptomatic treatment.
Fever	Control Group (n=129)	3 (2.33)	0 (0)	0.215	0.467	Relieved after antipyretic symptomatic treatment.
	Observation Group (n=137)	4 (2.92)	0 (0)			Relieved after antipyretic symptomatic treatment.
Hand-foot syndrome	Control Group (n=129)	5 (3.88)	1 (0.78)	0.857	0.281	Relieved after moisturizing care + dosage adjustment.
	Observation Group (n=137)	3 (2.19)	0 (0)			Relieved after moisturizing care.
Myelosuppression	Control Group (n=129)	4 (3.10)	0 (0)	0.007	0.605	Relieved after leukocyte-increasing symptomatic treatment.
	Observation Group (n=137)	4 (3.10)	0 (0)			Relieved after leukocyte-increasing symptomatic treatment.
Total	Control Group (n=129)	19 (14.73)	2 (1.55)	0.251	0.373	
	Observation Group (n=137)	16 (11.68)	1 (0.73)			

Note: Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 [1], with definitions as follows: Grade 1: Mild, no intervention required; Grade 2: Moderate, requiring mild to moderate intervention; Grade 3: Severe, requiring intensive intervention and affecting daily life; Grade 4: Life-threatening, requiring emergency treatment or causing organ function impairment. Serious Adverse Events (SAEs) were defined in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines [2], referring to any adverse medical event that results in death, is life-threatening, requires hospitalization/prolongation of hospitalization, causes persistent/significant disability/incapacity, or is a congenital anomaly/birth defect. Comparisons of categorical data between groups were performed using the chi-square (χ^2) test, with a two-tailed *P* value <0.05 considered statistically significant.

Table 8. Univariate analysis results (n (%))

	Death Group (n=173)	Survival Group (n=93)	OR	95% CI	P
Age			0.999	0.982-1.015	0.886
≤60 years	54 (31.21)	29 (31.18)			
>60 years	119 (68.79)	64 (68.82)			
TNM Stage			2.237	1.342-4.091	0.009
II	94 (54.34)	53 (56.99)			
III	63 (36.42)	36 (38.71)			
IV	16 (11.68)	4 (4.30)			
Smoking History			1.621	1.148-2.689	0.006
Yes	43 (24.86)	12 (12.90)			
No	130 (75.14)	81 (87.10)			
MVI Classification			1.422	1.030-1.962	0.032
M1	119 (68.79)	73 (78.49)			
M2	54 (31.21)	20 (21.51)			
Number of Intrahepatic Lesions			1.086	0.740-1.594	0.672
Solitary	32 (18.50)	21 (22.58)			
Multiple	141 (81.50)	72 (77.42)			
KPS Score			0.239	0.140-0.407	<0.001
70-90 points	15 (8.67)	45 (48.39)			
90 points	158 (91.33)	48 (51.61)			
Treatment Modality			1.466	1.087-1.978	0.012
TACE alone	92 (53.18)	37 (39.78)			
Huaier Granules + TACE	81 (46.82)	56 (60.22)			
Extrahepatic Metastasis			0.628	0.278-1.417	0.262
Yes	6 (3.47)	7 (7.53)			
No	167 (96.53)	86 (92.47)			
Post-treatment AST (U/L)	32.40±6.93	27.72±6.22	1.048	1.029-1.071	<0.001
Post-treatment ALT (U/L)	29.43±6.02	28.82±5.39	1.019	0.993-1.046	0.154
Post-treatment Alb (g/L)	37.04±3.15	36.63±3.15	1.016	0.970-1.054	0.501
Post-treatment TBil (μmol/L)	35.17±2.43	34.61±2.14	1.059	0.994-1.128	0.078

Note: TNM: Tumor Node Metastasis, MVI: Microvascular Invasion, KPS: Karnofsky Performance Status Scale, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, Alb: Albumin, TBil: Total bilirubin.

Table 9. Multivariate analysis results

	β	Std Error	OR	95% CI	P
TNM Stage	0.41	0.193	1.507	1.033-2.199	0.033
MVI Classification	0.263	0.179	1.301	0.916-1.849	0.142
KPS Score	-0.832	0.419	0.459	0.278-0.934	<0.001
Treatment Modality	1.055	0.208	2.872	1.909-3.321	<0.001
Smoking	0.148	0.189	1.159	0.800-1.680	0.435
Post-treatment AST	0.129	0.071	1.118	1.014-1.294	0.036

Note: TNM: Tumor Node Metastasis, MVI: Microvascular Invasion, KPS: Karnofsky Performance Status Scale, AST: Aspartate Aminotransferase.

ment (OR=2.872, 95% CI=0.278-0.934, P< 0.001) were independent risk factors for 3-year mortality. Higher KPS scores (OR=0.459, 95% CI=0.347-0.966, P<0.001) served as an independent protective factor, as shown in **Table 9**.

Predictive value of independent prognostic factors

ROC curves were used to test the predictive value of independent prognostic factors (TNM stage, post-treatment AST levels, KPS score, and treatment modality) for 3-year mortality. The AUC values for TNM stage, post-treatment AST levels, KPS score, and treatment modality were 0.572, 0.694, 0.699, and 0.572, respectively, as shown in **Figure 4**.

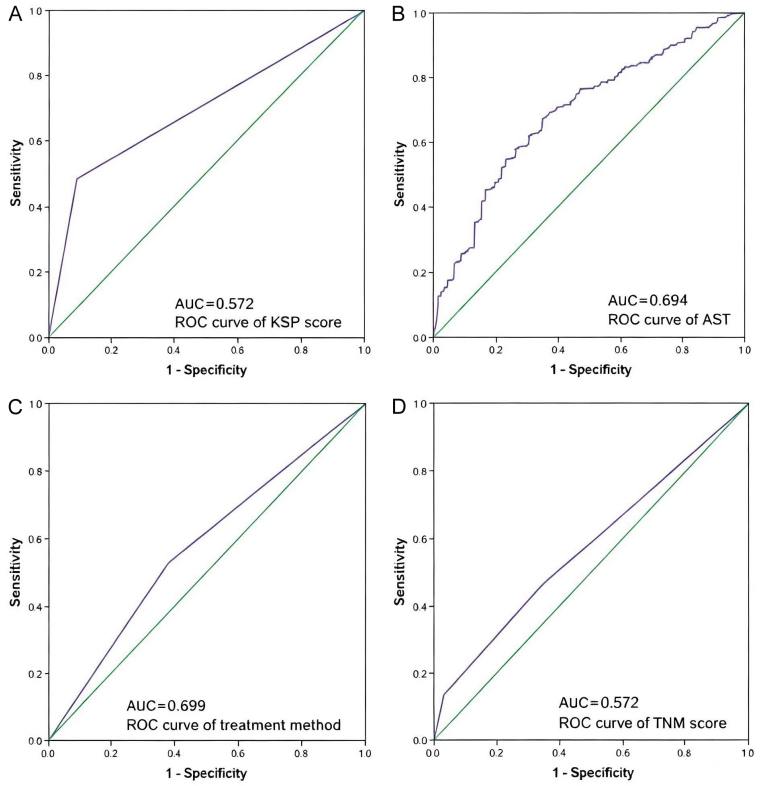


Figure 4. Predictive value of independent prognostic factors. A. ROC curve of KPS score predicting 3-year mortality. B. ROC curve of post-treatment AST predicting 3-year mortality. C. ROC curve of treatment modality predicting 3-year mortality. D. ROC curve of TNM stage predicting 3-year mortality. Note: KPS: Karnofsky Performance Status Scale, AST: Aspartate Aminotransferase, TNM: Tumor Node Metastasis.

Discussion

Besides traditional surgical resection, TACE currently serves as one of the primary treatments for primary hepatocellular carcinoma [16-18]. Most patients present with insidious onset and rapid progression, making early diagnosis difficult, and many cases are already in intermediate or advanced stages at detection. During postoperative TACE, cytotoxic agents and embolization can stress an already compromised liver and, in some patients, further erode hepatic reserve [18, 19]. This concern is amplified in resected HCC with MVI, where microscopic tumor thrombi have entered small intrahepatic vessels before adjuvant therapy. After arterial embolization, hypoxia can upregulate pro-angiogenic signaling - most notably Vascular Endothelial Growth Factor (VEGF) - in residual tumor cells, facilitating neovascularization and potentially increasing the risk of out-of-field recurrence if not countered [19-22]. In addition, TACE preferentially targets macroscopic arterialized lesions; micrometastatic deposits seeded via MVI, which may be poorly perfused or extra-segmental, often lie outside its direct cytotoxic reach [22, 23]. These biological and technical limitations help explain why early recurrence remains frequent after postoperative TACE in MVI-positive patients. Clinically, there is a rationale to pair TACE with agents that suppress hypoxia-driven angiogenesis and tumor cell survival while supporting liver function during the observation window, aiming to maintain antitumor pressure without unacceptable toxicity.

A comprehensive review of existing preclinical and clinical evidence reveals that the anticancer effects of Huaier Granules are mediated through multiple pathways and targets; however, their molecular mechanisms have not been fully elucidated, and relevant literature remains limited [23, 24]. The core mechanisms underlying the synergistic effect of Huaier Granules combined with TACE are as follows. First, in terms of angiogenesis inhibition, the main active components of Huaier Granules (such as polysaccharides and triterpenoids) can downregulate the expression of key pro-angiogenic molecules including HIF-1α, VEGF, and AEG-1, inhibit endothelial cell proliferation, and induce G0/G1 phase arrest, thereby blocking tumor neovascularization. Animal experiments have confirmed that Huaier polysaccharides at a dose of 2 mg/kg can significantly reduce tumor tissue microvessel density (MVD) and the number of stained microvessels [25]. This mechanism forms a precise synergy with TACE. The hypoxic microenvironment after TACE can induce overexpression of HIF-1α and VEGF, while Huaier Granules can specifically inhibit this compensatory angiogenic response and reduce blood supply to residual tumors [24]. Second, in terms of inducing apoptosis, Huaier extracts can upregulate the

Bax/Bcl-2 ratio, activate the caspase-9 and caspase-3 signaling pathways, and promote PARP cleavage to induce HCC cell apoptosis. Meanwhile, they can downregulate the anti-apoptotic gene MTDH, enhancing the sensitivity of tumor cells to hypoxia and chemotherapeutic drugs [25-27]. Third, at the immunomodulatory level, the proteoglycan components of Huaier Granules can activate the TLR4-NF-κB/MAPK signaling pathway, enhance macrophage phagocytosis and natural killer cell activity, promote lymphocyte proliferation, and improve the tumor immunosuppressive microenvironment [4]. Clinical studies have also confirmed that Huaier Granules can improve hepatic inflammatory status in patients with hepatitis B-related HCC, indirectly optimizing the immune microenvironment [3, 28, 29]. In terms of clinical synergistic value, although TACE can embolize tumor-feeding arteries, it can cause liver injury and reduce immune function. In contrast, Huaier Granules can compensate for these shortcomings by improving liver reserve function, enhancing immunity, and reversing tumor drug resistance, forming a synergistic effect of "local embolic ablation + systemic regulatory tumor suppression" [27, 30, 31]. A multicenter randomized controlled trial (RCT) involving 1,044 patients confirmed that Huaier Granules can reduce the postoperative recurrence rate of HCC by 33%, verifying the clinical value of its antitumor effect. However, mechanistic studies on the combination of Huaier Granules and TACE in MVI-positive populations remain scarce. The clinical efficacy data of this study will provide indirect evidence for this synergistic mechanism.

In our cohort, adding Huaier Granules to TACE was associated with a higher ORR than TACE alone. Notably, among patients who achieved an objective response, the proportion with M2 MVI was higher in the combination group than in the control group, suggesting that the response to the combination was not limited to milder (M1) disease. These clinical findings align with preclinical observations on Huaier's anti-angiogenic activity. Components of Huaier, including polysaccharides and triterpenes, have been reported to inhibit endothelial proliferation in vitro (e.g., G0/G1 arrest in human umbilical vein endothelial cells), which could dampen tumor-driven neovascularization [24, 32]. In mouse models, Huaier polysaccharides reduced tumor tissue MVD, with minimal stained microvessels observed at a 2 mg/kg dose. Mechanistically, downregulation of hypoxia-inducible and pro-angiogenic proteins - such as HIF-1α, AUF-1, VEGF, and AEG-1 - has been described [25, 30]. While these experiments are preclinical, they offer a biological rationale for the responses observed in MVI-positive patients, in whom hypoxia-driven angiogenesis can be pronounced after embolization. Clinically, we also observed improvements in liver function and a more favorable hepatic microenvironment in the combination group, which may facilitate therapy tolerance and sustain antitumor pressure when used with TACE. Taken together, the data support further evaluation of Huaier plus TACE in patients with MVI.

It should be noted, however, that the use of ORR as an exploratory endpoint in this study involves certain methodological considerations. In the adjuvant setting, there is a lack of measurable target lesions as defined by traditional RECIST criteria, and ORR assessment was primarily based on postoperative minimal residual lesions or potential recurrent foci, which may be subject to assessment bias. Thus, the ORR results are only intended to preliminarily indicate the inhibitory effect of the treatment on lesions and cannot be used as core evidence for efficacy. The core conclusions of this study are still based on the significant benefits in the primary endpoints of RFS and OS, combined with improvements in liver function, quality of life, and other indicators, collectively supporting the clinical value of Huaier Granules combined with TACE in postoperative HCC patients with MVI. Further large-sample and long-term follow-up studies are still needed to confirm the stability and long-term clinical benefit of this therapeutic regimen.

Postoperative survival favored the combination strategy. Within the 3-year window, both OS and RFS were longer with Huaier plus TACE than with TACE alone, and the 3-year cumulative recurrence rate was lower in the combination group. Although recurrence remained common in this high-risk cohort, the absolute difference at 3 years supports a clinically meaningful reduction in events. Because survival and recurrence directly capture treatment benefit in HCC, we prioritized these endpoints and interpreted them alongside response data. HRQoL was assessed with the EORTC QLQ-HCC18, which summarizes liver cancer-specific

symptoms and functioning (lower scores reflect fewer symptoms/better status) [33, 34]. Between-group differences in domain scores were evident by 3 months postoperatively, and overall HRQoL favored the combination group at both 1 and 3 months. These findings suggest that adding Huaier did not compromise short-term well-being and may alleviate symptom burden during early follow-up. Liver biochemistry also improved favorably. From baseline to post-treatment assessments, the combination group showed greater improvements in AST, ALT, albumin, and total bilirubin than the control group, without excess liver-related toxicity. Taken together, the survival, recurrence, HRQoL, and liver function data point in the same direction. That is, compared with TACE alone, Huaier plus TACE was associated with better disease control and maintained - or improved - patient-reported outcomes during early follow-up.

Safety analysis revealed that adverse events in both groups were mainly gastrointestinal reactions, fever, hand-foot syndrome, and myelosuppression, predominantly Grade 1-2 mild reactions. The incidence of Grade 3-4 severe adverse events was extremely low. All adverse events were successfully relieved after symptomatic treatment (antiemetic, antipyretic, leukocyte-increasing therapy) or nursing interventions (moisturizing care), and no serious safety incidents occurred. These findings indicate that adding Huaier Granules to TACE does not increase the risk of short-term adverse events, and the combination regimen exhibits favorable safety, providing a reliable safety guarantee for the clinical application of this combination therapy in high-risk postoperative HCC patients with MVI [31].

In multivariable Cox models, earlier TNM stage, lower post-treatment AST, and receipt of Huaier plus TACE were independently associated with lower 3-year mortality, while higher KPS was protective. Discrimination was modest: the AUC values were approximately 0.57 for TNM stage and treatment modality and ~0.69-0.70 for post-treatment AST and KPS, indicating limited to moderate prognostic value rather than high accuracy. Overall, in this postoperative HCC cohort with MVI, adding Huaier Granules to TACE was associated with lower 3-year recurrence, longer OS and RFS, and greater improvements in AST, ALT, albumin, and total bilirubin, without excess adverse events. These findings provide pragmatic support for considering the combination in this high-risk setting.

Although this study provides valuable insights for clinical practice, it is important to objectively acknowledge its limitations, as these factors may affect the robustness and generalizability of the conclusions to a certain extent. From an evidence-based medicine perspective, high-quality evidence supporting the use of Huaier Granules as adjuvant therapy for HCC remains relatively scarce. Most adjuvant treatment regimens recommended in major domestic and international HCC guidelines are based on Class I evidence from large-sample, multicenter RCTs, whereas studies on Huaier Granules are mostly small-sample retrospective analyses, with no broad consensus yet reached. Meanwhile, selection bias is difficult to completely avoid in a retrospective design - clinically, physicians may be more inclined to administer Huaier Granules combined with TACE to patients with better baseline conditions. Although multivariate models were used for adjustment, residual confounding may still exist. Additionally, this study did not adopt randomization, so it can only provide associative evidence rather than establishing a causal relationship between the treatment and outcomes. Future validation through large-sample, multicenter prospective RCTs will help enhance the credibility of the conclusions and provide more reliable evidence for clinical decision-making.

In summary, Huaier Granules combined with TACE shows promising clinical benefits in reducing recurrence, prolonging survival, improving liver function and HRQoL, with good safety, in postoperative MVI-positive HCC patients. Given the study limitations, prospective validation is needed to support its application in this high-risk population.

Disclosure of conflict of interest

None.

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