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ORIGINAL RESEARCH

Survival Benefit of Adjuvant Treatment with Huaier Granules Plus Lenvatinib in Hepatocellular Carcinoma Patients with Tumors Greater Than 5 cm After Radical Hepatectomy

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Video Abstract

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Background: The postoperative recurrence of hepatocellular carcinoma (HCC), influenced by various factors, including microvascular invasion (MVI), plays a critical role in the long-term prognosis following radical liver resection. This study investigated potential adjuvant treatment strategies for HCC patients who exhibit multiple recurrence factors after radical resection.

Methods: A retrospective analysis was conducted on data from 243 patients who underwent radical resection for HCC and exhibited high recurrence factors at the First Affiliated Hospital of Harbin Medical University. Some of these patients received postoperative adjuvant therapy with Huaier granules, lenvatinib, or a combination of both, while others did not receive any postoperative adjuvant therapy.

Results: Survival analysis showed a more favorable prognosis in the adjuvant Huaier granules and lenvatinib groups (all $P < 0.05$). Furthermore, when compared to monotherapy, the combination therapy group exhibited significantly improved overall survival (OS) ($P = 0.001$) and disease-free survival (DFS) ($P = 0.001$). Multivariate Cox regression analysis demonstrated that the addition of Huaier granules to lenvatinib was an independent protective factor associated with improved OS (hazard ratio (HR) = 0.777, 95% confidence interval (CI) = 0.616–0.980, $P = 0.033$) and DFS (HR = 0.753, 95% CI = 0.615–0.920, $P = 0.006$).

Conclusion: In this retrospective analysis, the combination of Huaier granules and lenvatinib as postoperative adjuvant therapy was associated with improved long-term prognosis in patients at high risk of HCC recurrence.

Keywords: hepatocellular carcinoma, Huaier granules, lenvatinib, recurrence, prognosis

Introduction

Primary liver cancer (PLC) is a prevalent malignancy worldwide. HCC is the most common subtype, accounting for 85% to 95% of PLC cases.[1] HCC ranks sixth among the most frequently occurring malignancies. With over 800,000 new cases reported annually worldwide, liver cancer poses a significant threat to human lives and well-being. The current

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primary treatment approach for HCC is a multidisciplinary comprehensive plan centered around surgeries, with hepatectomy considered the preferred choice for achieving a radical cure.[2] However, tumor recurrence following liver resection is a common occurrence, with a 5-year recurrence rate of 70%. The 5-year survival rate for patients who experience recurrence is less than 50%.[3] Tumor recurrence stands as the primary factor influencing the prognosis of radical surgery for HCC. Therefore, reducing the postoperative recurrence rate becomes crucial in improving overall treatment outcomes for liver cancer. Effectively preventing and treating liver cancer recurrence represents a critical clinical challenge that demands urgent attention, particularly for the long-term survival of liver cancer patients.

Postoperative adjuvant therapy for liver cancer encompasses various treatment options, with physicians designing specific plans based on the patient's condition and the type of cancer. Huaier, a traditional Chinese medicine with a history spanning 1600 years, has been extensively studied in clinical and laboratory settings, revealing its potential mechanisms in anti-cancer therapy. Huaier exerts anti-tumor effects through diverse mechanisms, including inhibition of proliferation, metastasis, angiogenesis, cancer stem cells, tumor-specific immunomodulation, and induction of tumor cell apoptosis.[4] The administration of Huaier granules following liver cancer surgery has demonstrated a significant increase in disease-free survival rate and reduction in recurrence rate. The efficacy of Huaier granules as an adjuvant therapy for postoperative liver cancer treatment has been recognized.[5]

Lenvatinib, a multitargeted inhibitor primarily targeting vascular endothelial growth factor receptor (VEGFR) 1–3, fibroblast growth factor receptor (FGFR) 1–4, platelet-derived growth factor receptor (PDGFR) α, β, RET, and KIT, represents an innovative molecular targeted agent.[6] The REFLECT study revealed that lenvatinib showed non-inferiority in overall survival rate and significant improvements in progression-free survival, time to progression, objective response rate, and safety compared to sorafenib in patients with advanced unresectable hepatocellular carcinoma (uHCC).[7] Lenvatinib, as a first-line targeted drug, has emerged more than a decade after the approval of sorafenib and has gained approval for the treatment of uHCC in the United States, European Union, China, Japan, and other countries.[8]

However, adverse events associated with lenvatinib may necessitate dose reduction in some patients, potentially impacting the therapeutic efficacy.[7] Considering the favorable tolerance of patients towards Huaier granules, a treatment regimen combining Huaier granules and lenvatinib may offer potential improvements in this context. Limited studies have investigated the use of Huaier granules or lenvatinib as adjuvant therapy following radical hepatectomy in HCC patients. Therefore, this study aimed to investigate the effectiveness of Huaier granules and lenvatinib in treating HCC after curative hepatectomy while also comparing the outcomes of the combined treatment regimen with monotherapy.

Patient Selection and Methodology

Patients

From January 2017 to January 2023, patients with HCC who received postoperative adjuvant treatment of Huaier granules, lenvatinib or combination therapy using Huaier granules plus lenvatinib at The First Affiliated Hospital of Harbin Medical University were prospectively enrolled.

Inclusion and Exclusion Criteria

Inclusion Criteria

Patients with a pathological diagnosis of HCC.

Underwent radical resection for HCC.

No prior anti-tumor treatment received before surgery.

Presence of a single lesion with a diameter greater than 5cm.

Exclusion Criteria

Other pathological types of liver cancer, including cholangiocarcinoma and mixed liver cancer.

Presence of distant metastases.

Development of tumor thrombus in the portal vein.

Inability to tolerate adverse events associated with Huaier granules or lenvatinib.

Patients with incomplete follow-up data.

Surgery and Adjuvant Treatment Protocols

Preoperatively, all patients underwent a multidisciplinary team discussion to determine the treatment plan. The resectability of HCC was assessed based on criteria such as tumor location and size, liver function, and future residual liver volume. Treatment options included both open and laparoscopic surgery. Patients with HCC were provided detailed information regarding the treatment protocols involving Huaier granules, lenvatinib, or combination therapy (Huaier granules plus lenvatinib) aimed at preventing tumor recurrence. The administration of Huaier granules involved a dosage of 20 g, three times a day. The dosage of lenvatinib was determined based on the patient's weight (≥ 60 kg: 12 mg; < 60 kg: 8 mg). In cases where patients experienced intolerable adverse events during medication administration, the dosage of the medication could be reduced (to 8 mg and 4 mg per day, or 4 mg every other day). If necessary, the administration of medication could also be discontinued.

Patient Follow-up

The postoperative follow-up schedule comprised evaluations every 3 months for two years following surgery. Each follow-up interview included assessments of liver function, AFP levels, and radiographic imaging. Tumor recurrence after resection was determined based on radiological evidence in conjunction with elevated AFP levels indicating recurrent lesions. The location, size, and number of recurrent hepatocellular carcinomas were evaluated using computed tomography (CT) or magnetic resonance imaging (MRI) during the postoperative follow-up period. All patients with hepatitis B took oral antiviral medications, and follow-up includes quantitative analysis of hepatitis B viral genes.

The Collected Variables Included the Following

Baseline characteristics: age, gender, virus infection status, presence of cirrhosis, Child-Pugh grade, levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB), total bilirubin (TBIL) and prothrombin time (PT).

Tumor-related variables: alpha fetoprotein (AFP) levels, presence of microvascular invasion (MVI), tumor diameter, number of tumors, tumor location, and tumor differentiation status (Edmonson tumor grades).

Follow-up information: survival status, tumor recurrence status, and adverse events experienced by the patients.

The cut-off values for all continuous variables were determined based on previous studies.

The study endpoints included OS and DFS. OS was defined as the duration from the date of liver resection to either the date of death or the final follow-up. DFS was calculated as the time interval from the date of surgery to the occurrence of initial HCC recurrence or the final follow-up.

Statistical Analysis

Using a Log rank test, OS and DFS were calculated using the Kaplan-Meier (K-M) analysis. Univariate and multivariate Cox proportional hazard regression models were employed to assess the potential risk factors affecting DFS and OS, with hazard ratios and 95% confidence intervals being reported for the results. Additionally, multivariate Cox regression analysis was conducted to determine whether combination therapy was an independent prognostic factor. The results with a P value < 0.1 (In Cox regression analysis, which aims to identify independent prognostic factors, the significance level differs from other statistical criteria. In this context, a p-value equal to 0.1 indicates an highly significant impact of the factor on prognosis. Therefore, a p-value less than or equal to 0.1 is considered statistically significant.) was considered statistically significant. All data were analyzed and sorted using SPSS version 25.0 and GraphPad 9.0 software.

Results

Clinical Data and Baseline Characteristics

Of the 603 patients with HCC who underwent radical hepatic resection at our hospital, 360 patients were excluded from the study. During the follow-up period, 35 patients (13%) were lost to follow-up. These patients were not included in the final analysis due to the need for post-treatment data. Contacting these patients was attempted via telephone calls and mailed letters, but no additional information could be obtained. The characteristics of patients lost to follow-up were similar to those included in the analysis, with no significant differences in age, gender, or other baseline characteristics (P > 0.05). The remaining 243 patients, who met the inclusion criteria, which included patients with a pathological diagnosis of HCC, underwent radical

resection for HCC, and had no prior anti-tumor treatment received before surgery, presence of a single lesion with a diameter greater than 5cm were enrolled in the study. Among them, researchers designated those who had not received any medications as the control group, 110 patients who received therapy with Huaier granules were set as the Huaier group, allocated 31 patients who received therapy with who received therapy with lenvatinib to the lenvatinib group and categorized 47 patients who received therapy with Huaier granules plus lenvatinib as the combination-therapy group.

Table 1 shows a comparison of the clinical data of the two groups. Baseline characteristics showed no statistical differences in the distribution of relevant variables among all groups (all P > 0.05). Patients with multiple tumors (21.81%, 24.54%, 32.25%, 29.78, P = 0.649), combined cirrhosis (43.63%, 52.72%, 58.06%, 61.70%, P = 0.297), and combined microvascular invasion (74.54%, 80.90%, 80.90%, 78.72%, P = 0.467) were more likely to receive drug adjuvant after hepatectomy (Table 1).

Table 1 Patient Baseline Demographic and Clinical Characteristics

Variable	Control	Huaier	Lenvatinib	Huaier Plus Lenvatinib	P value
Age (years), n (%)					P = 0.177
> 60	14 (25.45)	36 (32.72)	15 (48.38)	18 (38.29)	
≤ 60	41 (74.54)	74 (67.27)	16 (51.61)	29 (61.70)	
Gender, n (%)					P = 0.914
Female	10 (18.18)	22 (20.00)	7 (22.58)	11 (23.40)	
Male	45 (81.81)	88 (80.00)	24 (77.41)	36 (76.59)	
Virus infection, n (%)					P = 0.107
(–)	15 (27.27)	22 (20.00)	5 (16.12)	9 (19.14)	
HBV-DNA	39 (70.90)	86 (78.18)	22 (70.96)	34 (72.34)	
HCV-DNA	1 (1.81)	2 (1.81)	4 (12.90)	4 (8.51)	
AFP (IU/mL), n (%)					P = 0.632
> 400	18 (32.72)	45 (40.90)	14 (45.16)	15 (31.91)	
≤ 400	37 (67.27)	65 (59.09)	17 (54.83)	32 (68.08)	
ALT (U/L), n (%)					P = 0.217
> 40	15 (27.27)	29 (26.36)	7 (22.58)	20 (42.55)	
≤ 40	40 (72.72)	81 (73.63)	24 (77.41)	27 (57.44)	
AST (U/L), n (%)					P = 0.271
> 40	19 (34.54)	33 (30.00)	8 (25.80)	23 (48.93)	
≤ 40	36 (65.45)	77 (70.00)	23 (74.19)	24 (51.06)	
ALB (g/L), n (%)					P = 0.875
> 34	51 (92.72)	98 (89.09)	30 (96.77)	43 (91.48)	
≤ 34	4 (7.27)	12 (10.90)	1 (3.22)	4 (8.51)	
TBIL (mmol/L), n (%)					P = 0.139
> 21	11 (20.00)	20 (18.18)	3 (9.67)	11 (23.40)	
≤ 21	44 (80.00)	90 (81.81)	28 (90.32)	36 (76.59)	
PT (S), n (%)					P = 0.219
> 13	9 (16.36)	13 (11.81)	2 (6.45)	9 (19.14)	
≤ 13	46 (83.63)	97 (88.18)	29 (93.54)	38 (80.85)	
Cirrhosis, n (%)					P = 0.297
No	31 (56.36)	52 (47.27)	13 (41.93)	18 (38.29)	
Yes	24 (43.63)	58 (52.72)	18 (58.06)	29 (61.70)	
Child-Pugh, n (%)					P = 0.758
A	51 (92.72)	104 (94.54)	30 (96.77)	46 (97.87)	
B	4 (7.27)	6 (5.45)	1 (3.22)	1 (2.12)	
Tumor diameter (cm), n (%)					P = 0.708
> 10	12 (21.81)	21 (19.09)	0 (0.00)	9 (19.14)	
≤ 10	43 (78.18)	89 (80.90)	31 (100.00)	38 (80.85)	

(*Continued*)

Table 1 (Continued).

Variable	Control	Huaier	Lenvatinib	Huaier Plus Lenvatinib	P value
Tumor number, n (%)					P = 0.649
1	43 (78.18)	83 (75.45)	21 (67.74)	33 (70.21)	
≥ 2	12 (21.81)	27 (24.54)	10 (32.25)	14 (29.78)	
MVI, n (%)					P = 0.467
M0	14 (25.45)	21 (19.09)	5 (16.12)	10 (21.27)	
M1	26 (47.27)	58 (52.72)	15 (48.38)	17 (36.17)	
M2	15 (27.27)	31 (28.18)	11 (35.48)	20 (42.55)	
Tumor differentiation, n (%)					P = 0.187
> G2	32 (58.18)	55 (50.00)	16 (51.61)	28 (59.57)	
≤ G2	23 (41.81)	55 (50.00)	15 (48.38)	19 (40.42)	

Notes: Bold values indicate statistical significance (P < 0.05).
Abbreviations: AST, aspartate aminotransferase; ALB, albumin; ALT, alanine aminotransferase; PT, prothrombin time; TBIL, total bilirubin; AFP, alpha fetoprotein; HBV-DNA, hepatitis B virus-deoxyribonucleic acid; HCV-DNA, hepatitis C virus-deoxyribonucleic acid; MVI, microvascular invasion; G, Grading.

Overall Survival and Disease-Free Survival Analysis

The number of deaths within 2 years postoperatively in the control group, Huaier granule group, lenvatinib group, and combination-therapy group was 29, 37, 10, and 9, respectively. The number of recurrence patients was 33, 49, 13, and 12, respectively.

The Kaplan-Meier curves demonstrated that the drug adjuvant group had a significantly higher 2-year overall survival rate and disease-free recurrence rate than the control group. Additionally, when compared to monotherapy, the combination-therapy group exhibited a higher 2-year overall survival rate and disease-free recurrence rate (2-year survival rates: 47.3%, 66.4%, 67.7%, 80.9%, respectively, P = 0.001; 2-year recurrence rates: 40.0%, 55.5%, 58.1%, 74.5% respectively, P = 0.001) (Figure 1A and B). The results with a P-value < 0.05 indicate statistically significant differences.

Univariable and Multivariable Cox Regression Analysis

Six potential prognostic variables for OS and DFS were selected based on univariate Cox analysis, including preoperative AFP level, tumor diameter, tumor number, tumor differentiation status, MVI, and treatment options. Variables with a P < 0.1 in univariable analysis were incorporated into multivariable Cox regression analysis (Tables 2 and 3).

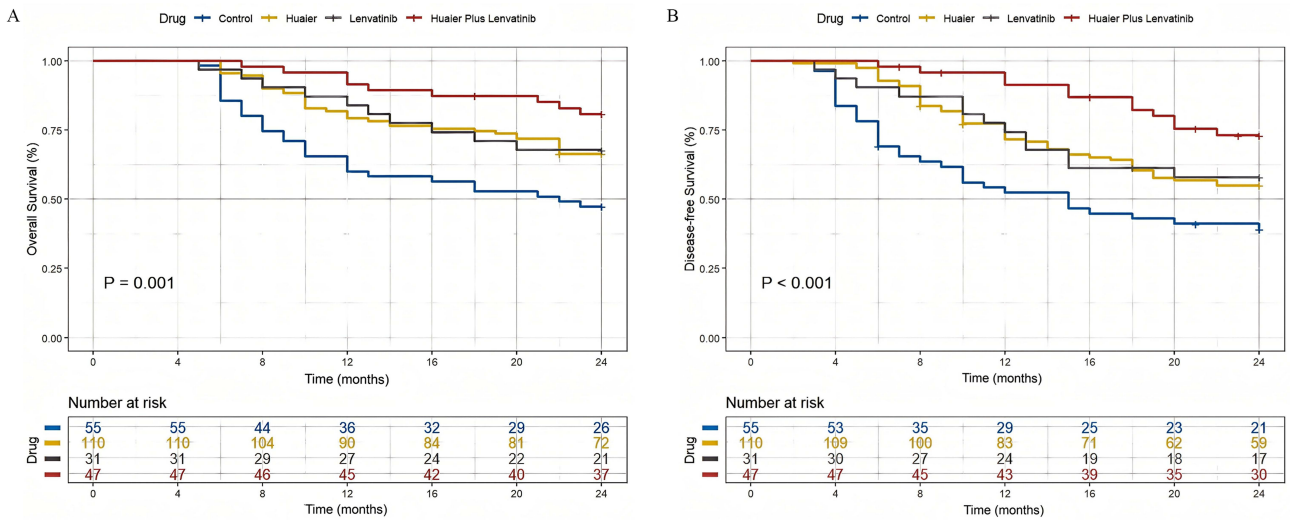

Figure 1 Kaplan-Meier analysis for survival in patients with HCC after radical hepatectomy. (**A**) Overall survival (OS). (**B**) Disease-free survival (DFS).

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Table 2 Univariate Analyses of Prognostic Factors for Overall Survival (OS) and Disease-Free-Survival (DFS)

Variables	Univariate Analysis (OS)		Univariate Analysis (DFS)	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, years	1.006 (0.985–1.028)	0.563	0.993 (0.975–1.012)	0.487
Gender, (Female vs Male)	0.713 (0.402–1.266)	0.248	0.749 (0.451–1.242)	0.263
Virus infection, (Yes vs No)	0.850 (0.515–1.404)	0.526	0.805 (0.549–1.181)	0.267
AFP, (IU/mL) (> 400 vs ≤ 400)	1.001 (1.000–1.001)	0.004	1.000 (1.000–1.001)	0.044
ALT, (U/L) (> 40 vs ≤ 40)	0.998 (0.991–1.005)	0.550	1.001 (0.995–1.006)	0.808
AST, (U/L) (> 40 vs ≤ 40)	1.003 (0.997–1.008)	0.325	1.003 (0.999–1.008)	0.175
ALB, (g/L) (> 34 vs ≤ 34)	0.983 (0.937–1.031)	0.479	1.001 (0.960–1.044)	0.957
TBIL, (mmol/L) (> 21 vs ≤ 21)	1.002 (0.983–1.021)	0.822	0.996 (0.978–1.015)	0.704
PT, (S) (> 13 vs ≤ 13)	1.140 (0.923–1.408)	0.223	1.111 (0.919–1.344)	0.278
Cirrhosis, (Yes vs No)	0.929 (0.607–1.422)	0.735	0.926 (0.634–1.353)	0.690
Child-Pugh, (A vs B)	1.192 (0.483–2.943)	0.703	1.623 (0.790–3.338)	0.188
Tumor diameter (cm), (> 10 vs ≤ 10)	5.262 (3.375–8.203)	<0.001	3.606 (2.357–5.516)	<0.001
Tumor number, (1 vs ≥ 2)	0.521 (0.312–0.869)	0.013	0.584 (0.381–0.895)	0.014
Microvascular invasion, (Yes vs No)	2.491 (1.248–4.971)	0.010	3.078 (1.604–5.904)	<0.001
Tumor differentiation, (> G2 vs ≤ G2)	1.316 (1.137–1.524)	<0.001	1.220 (1.074–1.386)	0.002
Treatment options, (Huaier vs Control)	0.522 (0.321–0.849)	0.009	0.567 (0.365–0.882)	0.012
Treatment options, (Lenvatinib vs Control)	0.499 (0.243–1.025)	0.058	0.536 (0.282–1.019)	0.057
Treatment options, (Huaier Plus Lenvatinib vs Control)	0.269 (0.127–0.569)	0.001	0.282 (0.145–0.546)	<0.001

Abbreviations: AST, aspartate aminotransferase; ALB, albumin; ALT, alanine aminotransferase; PT, prothrombin time; TBIL, total bilirubin; AFP, alpha fetoprotein; CI, confidential interval; HR, hazard ratio; G, Grading.

Table 3 Multivariate Analyses of Prognostic Factors for Overall Survival (OS) and Disease-Free-Survival (DFS)

Variables	Multivariable Analysis (OS)		Multivariable Analysis (DFS)	
	HR (95% CI)	P value	HR (95% CI)	P value
Tumor diameter (cm), (> 10 vs ≤ 10)	5.100 (3.148–8.261)	<0.001	2.939 (1.853–4.662)	<0.001
Microvascular invasion, (Yes vs No)			2.171 (1.103–4.274)	0.025

(*Continued*)

Table 3 (Continued).

Variables	Multivariable Analysis (OS)		Multivariable Analysis (DFS)	
	HR (95% CI)	P value	HR (95% CI)	P value
Tumor differentiation, (> G2 vs ≤ G2)	1.491 (1.146–1.941)	0.003	1.383 (1.081–1.770)	0.010
Treatment options, (Huaier vs Control)	0.408 (0.249–0.671)	<0.001	0. 450 (0.287–0.706)	0.001
Treatment options, (Lenvatinib vs Control)	0.652 (0.310–1.369)	0.258	0.559 (0.290–1.079)	0.083
Treatment options, (Huaier Plus Lenvatinib vs Control)	0.243 (0.115–0.516)	<0.001	0.243 (0.125–0.472)	<0.001

Abbreviations: CI, confidential interval; HR, hazard ratio; G, Grading.

Univariate and multivariate analyses revealed that tumor diameter >10 cm (P < 0.001) and tumor differentiation grade > G2 (P = 0.003) were identified as independent risk factors for postoperative survival. The combination-therapy group post-surgery demonstrated the best survival outcome (HR (95% CI): 0.243 (0.115–0.516); P < 0.001). Treatment with Huaier granules monotherapy was superior to the control group (HR (95% CI): 0.408 (0.249–0.671); P < 0.001). The study also suggested that lenvatinib monotherapy could improve postoperative survival rates (HR (95% CI): 0.652 (0.310–1.369); P = 0.258), but a P-value > 0.05 indicates a lack of statistical significance (Table 3).

Tumor diameter >10 cm (P < 0.001), tumor differentiation grade > G2 (P = 0.010), and conventional pathology showing microvascular invasion (P = 0.025) were identified as independent risk factors for postoperative recurrence. The combination-therapy group post-surgery demonstrated the best outcome in reducing postoperative recurrence (HR (95% CI): 0.243 (0.125–0.472); P < 0.001). Treatment with Huaier granules monotherapy was superior to the control group in reducing recurrence (HR (95% CI): 0.450 (0.287–0.706); P = 0.001). The study suggested that lenvatinib monotherapy could reduce postoperative recurrence rates (HR (95% CI): 0.559 (0.290–1.079); P = 0.083), but a P-value > 0.05 indicates a lack of statistical significance (Table 3).

Three regression models were established in this study to minimize the influence of confounding factors on study outcomes. Different therapeutic regimens were analyzed as a single variable to assess their effects on OS and DFS (Table 4 MODEL 1). Multivariable Cox regression analysis was performed to incorporate variables associated with study

Table 4 Predictive Model of Determinants Associated with Overall Survival (OS) and Disease-Free-Survival (DFS)

	Huaier vs Control	Lenvatinib vs Control	Huaier Plus Lenvatinib vs Control
Analysis of associated factors (OS) HR (95% CI) P value			
MODEL 1	0.522 (0.321–0.849) 0.009	0.499 (0.243–1.025) 0.058	0.269 (0.127–0.569) 0.001
MODEL 2	0.408 (0.249–0.671) <0.001	0.652 (0.310–1.369) 0.258	0.243 (0.115–0.516) <0.001
MODEL 3	0.317 (0.187–0.536) <0.001	0.555 (0.262–1.174) 0.123	0.194 (0.090–0.417) <0.001
Analysis of associated factors (DFS) HR (95% CI) P value			
MODEL 1	0.567 (0.365–0.882) 0.012	0.536 (0.282–1.019) 0.057	0.282 (0.145–0.546) <0.001
MODEL 2	0. 450 (0.287–0.706) 0.001	0.559 (0.290–1.079) 0.083	0.243 (0.125–0.472) <0.001
MODEL 3	0.410 (0.258–0.650) <0.001	0.537 (0.277–1.040) 0.065	0.220 (0.112–0.432) <0.001

Notes: Variables in MODEL1: Treatment options. Variables in MODEL2: Tumor diameter, Microvascular invasion, Tumor differentiation, Treatment options. Variables in MODEL3: Age, Gender, preoperative AFP, Tumor diameter, Tumor number, Microvascular invasion, Tumor differentiation, Treatment options.
Abbreviations: CI, confidential interval; HR, hazard ratio; G, Grading.

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outcomes into the regression model (Table 4 MODEL 2). To further mitigate potential confounding, demographic parameters and variables with established prognostic relevance to HCC postoperative outcomes were incorporated into regression models (Table 4 MODEL 3), including Age, Gender, preoperative AFP, Tumor diameter, Tumor number, Microvascular invasion, Tumor differentiation, Treatment options.[9,10] The outcomes in the regression models are concordant, indicating that the aforementioned results exhibit relative stability.

Comparison of OS and DFS in Patients with MVI

In this cohort, a total of 193 patients were found to have concomitant MVI based on the pathological report after liver resection. Compared to the control group, the drug adjuvant group exhibited a higher 2-year overall survival rate and disease-free recurrence rate; compared to the monotherapy, the combination-therapy group exhibited a higher 2-year overall survival rate and disease-free recurrence rate (2-year survival rates were 43.9%, 61.8%, 61.5%, 75.7% respectively, P = 0.008; 2-year disease-free survival rates were 31.7%, 50.6%, 50.0%, 67.6% respectively, P = 0.001) (Figure 2A and B).

Adverse Events of Adjuvant Therapy

During follow-up, medical staff monitored all patients for drug safety. Among the 188 patients who received adjuvant therapy over two years, 57 patients experienced adverse events. Adverse drug reactions were reported in 19 (17.27%), 18 (58.06%), and 20 (42.55%) patients in the Huaier group, lenvatinib group, and Huaier plus lenvatinib combination therapy group, respectively (Table 5). The most frequent adverse events included diarrhea (60.0%), hypertension (32.7%), decreased appetite (21.81%), and PPES (16.36%). Medical staff observed life-threatening adverse events in 2 patients (3.6%), which involved gastrointestinal bleeding in both cases. Medical staff classified adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v 5.0. Analysis of mortality causes revealed that no fatal adverse events occurred. Non-oncological causes included cardiovascular events, renal failure, and other conditions (Table 6). The study suggested that lenvatinib caused most adverse events in the combination therapy group. However, symptoms could be alleviated by reducing the dosage or implementing symptomatic treatment options. Adverse drug reactions should be managed with differentiated strategies based on expert consensus recommendations.[11]

Discussion

HCC is the predominant form of primary liver cancer globally. Despite advancements in treatment, HCC remains highly invasive, leading to high recurrence rates and poor postoperative survival even in the early and intermediate stages after radical hepatectomy. To improve the prognosis following liver cancer surgery, various postoperative adjuvant options

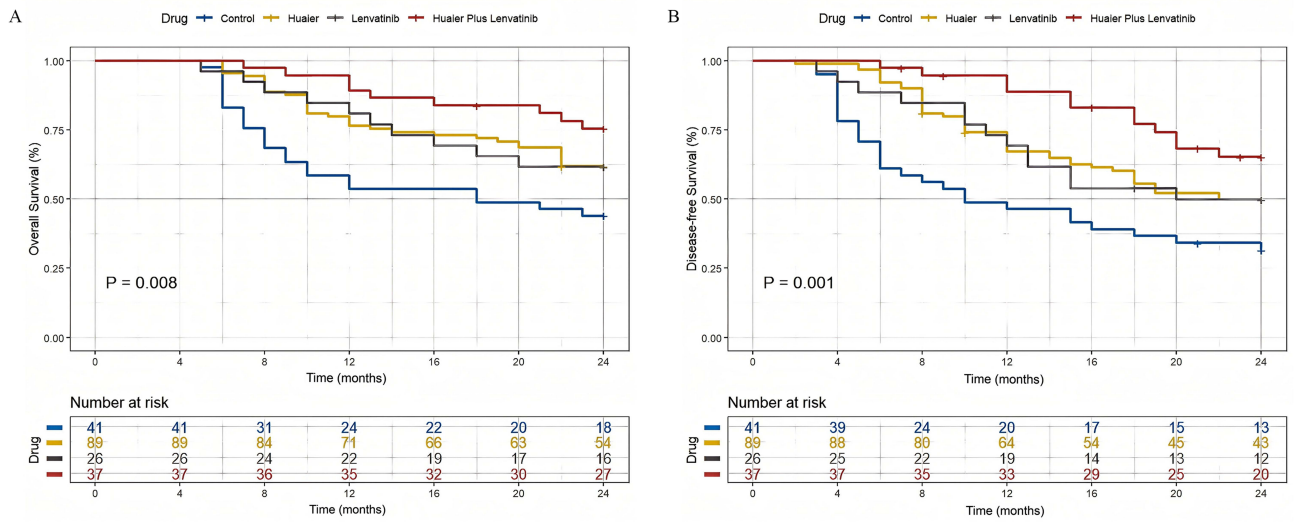

Figure 2 Kaplan-Meier analysis for survival in patients with HCC and MVI after radical hepatectomy. (**A**) Overall survival (OS). (**B**) Disease-free survival (DFS).

Table 5 Incidence and Proportional Distribution of Adverse Events Across Therapeutic Arms

Adverse Events	Adjuvant Therapy (188)			
	All (57)	Huaier (110)	Lenvatinib (31)	Huaier Plus Lenvatinib (47)
Incidence rate		19 (17.27%)	18 (58.06%)	20 (42.55%)
Hypertension	18	1 (0.91%)	10 (32.25%)	7 (14.89%)
Diarrhoea	33	17 (15.45%)	6 (19.35%)	10 (21.28%)
PPES	9	0	3 (9.68%)	6 (12.77%)
Decreased appetite	12	2 (1.82%)	7 (22.58%)	3 (6.38%)
Others	4	0	3 (9.68%)	1 (2.13%)

Abbreviation: PPES, palmar-plantar erythrodysesthesia syndrome.

Table 6 Disclosure of Mortality Causality

	Control	Huaier	Lenvatinib	Huaier Plus Lenvatinib
Total number of deaths	29	37	10	9
Disease progression	23 (79.31%)	25 (67.57%)	7 (70.00%)	5 (55.55%)
Other causes	6 (20.68%)	12 (32.43%)	3 (30.00%)	4 (44.44%)

have emerged including transarterial chemoembolization (TACE), radiation therapy, targeted therapy, immunotherapy, antiviral therapy, traditional Chinese medicine, and other modalities.

Huaier, as a representative of traditional Chinese medicine, has garnered considerable interest among researchers due to its advantageous characteristics, such as safety, minimal adverse events, and its multi-target approach to cancer treatment. Huaier exhibits various mechanisms of action, including the inhibition of tumor neovascularization by suppressing the proliferation of vascular endothelial cells, induction of apoptosis in cancer cells through activation of the Caspase pathway, enhancement of immune function, and improvement of anti-tumor efficacy by modulating the activity of T-lymphocyte subsets, natural killer cells, and multiple cytokines.[4] The immunomodulatory effects of Huaier have been empirically validated and demonstrated to exert therapeutic benefits in the management of various immune-related pathologies, including neoplastic disorders. Accumulating evidence indicates that Huaier exerts immunomodulatory effects on key immune cell populations, including natural killer (NK) cells, T lymphocytes, and B lymphocytes. NK cells, as critical cytotoxic effectors of the innate immune system, are indispensable for antitumor immunity. Pharmacological administration of Huaier or its bioactive derivatives has been demonstrated to enhance both the numerical abundance and cytotoxic activity of NK cells. In murine models, the Huaier-derived polysaccharide TP-1 markedly increased splenic NK cell populations, highlighting its potential as an immunotherapeutic agent.[12] In rat models of HCC recurrence following liver transplantation, administration of Huaier polysaccharides significantly elevated peripheral $CD4^+$ and $CD8^+$ T-cell frequencies. Experimental analyses further revealed that Huaier treatment downregulated $Foxp3^+$ Treg populations in peripheral blood and facilitated the breakdown of immune tolerance to malignant cells.[13] Emerging clinical studies have reported significantly elevated serum IgM levels in patients with HCC receiving Huaier therapy. However, the mechanistic role of Huaier in IgM immunomodulation remains inconclusive.[14] A multicenter, randomized clinical trial has confirmed the efficacy of Huaier granules as a postoperative treatment for liver cancer, demonstrating its ability to reduce recurrence and prolong survival effectively.[5]

Lou et al conducted a study investigating the impact of Huaier granules on the overall survival of patients following radical hepatectomy for liver cancer. The results revealed significant improvements in OS at 1-year, 3-year, and 5-year intervals between the control group and the Huaier granules group. Additionally, the 5-year RFS rate was higher in the Huaier granules group compared to the control group, providing further evidence of the significant efficacy of Huaier granules in improving OS and DFS after HCC resection.[15]

In a cohort study by Wang et al,[16] the efficacy of Huaier granules after hepatectomy for liver cancer in preventing tumor recurrence was examined. The study revealed favorable outcomes, further supporting the potential benefits of Huaier granules in improving patient prognosis following surgical resection of HCC. Numerous studies have consistently demonstrated that oral administration of Huaier granules after hepatectomy for liver cancer can effectively prevent tumor recurrence and improve overall survival. In line with these findings, our present study revealed that compared to the control group, the Huaier group exhibited significantly higher 2-year overall survival (47.3% vs 66.4%, P = 0.007) and disease-free survival rates (40.0% vs 55.5%, P = 0.010) (Figure 1).

Targeted therapy is a specialized approach to cancer treatment that specifically targets molecules or pathways involved in the growth and spread of cancer cells. Unlike traditional chemotherapy, which can harm healthy and cancer cells, targeted therapy aims to attack cancer cells while minimizing damage to normal cells selectively.In recent years, targeted therapy has also been used as adjuvant therapy in patients with HCC after hepatectomy. A randomized Phase III non-inferiority trial for advanced unresectable hepatocellular carcinoma demonstrated the efficacy of lenvatinib. Further advancements in molecular targeted therapy have identified lenvatinib as a new treatment option for unresectable hepatocellular carcinoma. Lenvatinib has become the second first-line targeted drug approved for treating of advanced hepatocellular carcinoma, following sorafenib.[7]

Tumor recurrence plays a critical role in determining postoperative survival outcomes. In efforts to enhance the postoperative survival of HCC patients, molecular targeted therapy has been employed as an adjuvant treatment approach. A phase III randomized trial demonstrated that adjuvant therapy with Sorafenib following curative resection for HCC was ineffective in improving clinical outcomes.[17] On the other hand, relevant evidence has confirmed the efficacy of lenvatinib as an adjuvant therapy for liver cancer, showing improvements in OS and RFS following postoperative application.[18,19]

This study assessed the efficacy of combining Huaier granules with lenvatinib as adjuvant therapy following curative resection for HCC. A total of 243 patients who met the inclusion and exclusion criteria were included in this survival and recurrence follow-up study after curative liver resection. Our study results indicate that compared to the control group, both Huaier granules and lenvatinib significantly prolonged the 2-year OS (47.3% vs 66.4%; 47.3% vs 67.7%), as well as DFS (40.0% vs 55.5%; 40.0% vs 58.1%). However, COX analysis suggested that lenvatinib monotherapy could prolong survival in postoperative liver cancer patients compared to the control group, but with P > 0.05, it did not reach statistical significance. This result may be due to the small sample size. Additionally, the results indicate that the combined treatment regimen has the best therapeutic effect.

The prevalence of MVI in HCC patients is relatively high, ranging from 15% to 57%, and is considered an essential factor contributing to postoperative recurrence.[20] Vascular endothelial growth factor (VEGF), a potent pro-angiogenic factor, is crucial in promoting vascular endothelial cells proliferation, migration, and anti-apoptosis. Additionally, it acts as a specific mitogen for vascular endothelial cells, enhancing vascular permeability.[21] Huaier has been found to inhibit the expression of VEGF in a dose-dependent manner, thereby reducing tumor angiogenesis.[4,22]

In a study by Hua et al,[23] the combination treatment group demonstrated a slightly higher survival rate compared to the TACE group, along with a lower recurrence rate when comparing the 3-year survival rate and 1–3 year recurrence rates between the TACE + Huaier granules group and the TACE group. This study suggested that the use of Huaier granules after radical hepatectomy in patients with HCC and MVI can reduce tumor recurrence. Furthermore, our study indicated that using Huaier granules significantly improved overall survival (43.9% vs 61.8%, P = 0.016) and disease-free survival (31.7% vs 50.6%, P = 0.006) in HCC patients with MVI.

Lenvatinib, by suppressing the development of tumor neovascularization, has demonstrated its ability to inhibit tumor growth, proliferation, and metastasis.[8] Consequently, numerous studies have suggested that lenvatinib exhibits favorable therapeutic effects in patients with HCC and MVI. For instance, Dai et al conducted a study involving patients with HCC who underwent curative liver resection and were found to have MVI on pathological examination.The lenvatinib group demonstrated a more significant improvement in OS and RFS. Multivariate analysis indicated that adjuvant treatment with lenvatinib was an independent prognostic factor for improved OS and RFS.[18] A retrospective study analyzed the survival outcomes of postoperative adjuvant use of lenvatinib in patients with HCC who underwent R0 resection and had histologically confirmed MVI. The lenvatinib group showed significant improvements in OS and TTR. The study

compared prognostic outcomes among different MVI subgroups and found that lenvatinib treatment had a significant effect when MVI = M1, with similar results observed for MVI = M2. Bai et al concluded that lenvatinib could reduce the recurrence rate and improve long-term survival in patients with HCC and MVI after curative liver resection.[19] Moreover, this study demonstrated that patients receiving combination therapy in comparison to other groups showed significant improvement in OS (P = 0.008) and DFS (P = 0.001).

Adverse events during the clinical use of drugs are an essential factor for evaluating drug effectiveness. In a randomized controlled experiment, Chen et al[5] found that patients had outstanding tolerance to Huaier granules, which initially confirmed the safety of Huaier granules. Most important, they found that all reactions were mild and tolerable. Although lenvatinib has achieved significant clinical effects in the III phase clinical trial, its adverse events are a major factor affecting the curative effect. A study by Kudo et al[6] found that adverse events occurred in 99% of patients who received lenvatinib. The most common any-grade adverse events were hypertension, which accounted for 42%, and other common adverse events were diarrhea (39%), decreased appetite (34%), and decreased body weight (31%). Expert consensus suggests employing different measures based on specific adverse events.[9]

Adverse events resulting from drug treatment can significantly impact the quality of life and treatment compliance. The safety profiles of Huaier granules and lenvatinib highlight their potential as well-tolerated adjuvant therapies in patients with HCC. In our study, adverse events were observed in the combination treatment group, potentially attributable to the concurrent use of lenvatinib. Throughout our research, these adverse events were managed by adjusting drug dosage or implementing symptomatic treatment. This study found that two patients in the lenvatinib group experienced gastrointestinal bleeding, which was a life-threatening adverse event. Some studies suggested that antiangiogenic agents were associated with gastrointestinal bleeding.[24] It has been suggested that Huaier granules may possess specific detoxification effects,[25] which could mitigate adverse events associated with lenvatinib. No adverse gastrointestinal bleeding events were observed in the combination therapy group, which may have confirmed the viewpoint above—however, this specific aspect needed to be more evident in our study. Adverse events remain a key focus of our attention.

Although our research has demonstrated the improved prognosis associated with the combination of Huaier granules and lenvatinib as adjuvant therapy, it is essential to acknowledge the limitations of this study: First, being a single-center study, the results may be subject to biases and have limited generalizability compared to multi-center studies. Second, the relatively small sample size of patients may impact the statistical power and generalizability of the findings. Therefore, in future studies, we aim to address these limitations by increasing the sample size and extending the duration of follow-up. Third, given the inherent limitations of retrospective analyses, prospective randomized controlled trials are warranted to establish the observed association between combination therapy and improved clinical outcomes, and to confirm its therapeutic benefits in patients with hepatocellular carcinoma.

Conclusions

In conclusion, this retrospective study observed an association between the combined use of Huaier Granules and Lenvatinib and reduced postoperative recurrence rates, as well as improved long-term survival outcomes, in patients with HCC following radical hepatectomy. However, large-scale multicenter randomized controlled trials and prospective studies with rigorous methodologies are warranted to validate the therapeutic efficacy of this combination regimen.

Highlights

- Exploring effective adjuvant therapies for hepatocellular carcinoma.
- Investigation of independent risk factors for postoperative recurrence of hepatocellular carcinoma.
- Comparison of adverse events of Huaier and lenvatinib as adjuvant therapies.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics Statement

The study was approved by the Research Ethics Committee of The First Affiliated Hospital of Harbin Medical University. The procedures used in this study adhere to the tenets of the Declarations of Helsinki. All of the patients agree that their clinical details and accompanying images are published.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest pertain to this work.

References

1. Zhou M, Wang H, Zeng X, et al. Mortality, morbidity, and risk factors in China and its provinces, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2019;394(10204):1145–1158. doi:10.1016/S0140-6736(19)30427-1
2. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet*. 2018;391(10127):1301–1314. doi:10.1016/S0140-6736(18)30010-2
3. Fukami Y, Kaneoka Y, Maeda A, et al. Liver resection for multiple hepatocellular carcinomas: a Japanese Nationwide Survey. *Ann Surg*. 2020;272 (1):145–154. doi:10.1097/SLA.0000000000003192
4. Song X, Li Y, Zhang H, Yang Q. The anticancer effect of Huaier (Review). *Oncol Rep*. 2015;34(1):12–21.
5. Chen Q, Shu C, Laurence AD, et al. Effect of Huaier granule on recurrence after curative resection of HCC: a multicentre, randomised clinical trial. *Gut*. 2018;67(11):2006–2016. doi:10.1136/gutjnl-2018-315983
6. Kudo M. Lenvatinib may drastically change the treatment landscape of hepatocellular carcinoma. *Liver Cancer*. 2018;7(1):1–19. doi:10.1159/000487148
7. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised Phase 3 non-inferiority trial. *Lancet*. 2018;391(10126):1163–1173. doi:10.1016/S0140-6736(18)30207-1
8. Zhao Y, Zhang YN, Wang KT, Chen L. Lenvatinib for hepatocellular carcinoma: from preclinical mechanisms to anti-cancer therapy. *Biochim Biophys Acta Rev Cancer*. 2020;1874(1):188391. doi:10.1016/j.bbcan.2020.188391
9. Xia Y, Yan ZL, Xi T, et al. A case-control study of correlation between preoperative serum AFP and recurrence of hepatocellular carcinoma after curative hepatectomy. *Hepatogastroenterology*. 2012;59(119):2248–2254. doi:10.5754/hge11978
10. Hu XS, Yang HY, Leng C, Zhang ZW. Postoperative outcomes and recurrence patterns of intermediate-stage hepatocellular carcinoma dictated by the sum of tumor size and number. *World J Gastroenterol*. 2022;28(44):6271–6281. doi:10.3748/wjg.v28.i44.6271
11. Kim BH, Yu SJ, Kang W, et al. Expert consensus on the management of adverse events in patients receiving lenvatinib for hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2022;37(3):428–439. doi:10.1111/jgh.15727
12. Li C, Wu X, Zhang H, et al. A Huaier polysaccharide inhibits hepatocellular carcinoma growth and metastasis. *Tumour Biol*. 2015;36 (3):1739–1745. doi:10.1007/s13277-014-2775-2
13. Zhou L, Pan LC, Zheng YG, et al. Reduction of FoxP3+ Tregs by an immunosuppressive protocol of rapamycin plus Thymalfasin and Huaier extract predicts positive survival benefits in a rat model of hepatocellular carcinoma. *Ann Transl Med*. 2020;8(7):472. doi:10.21037/atm.2020.03.129
14. Ma Y, Wang C, Zhang Q, Peng X, Feng Y, Meng X. The effects of polysaccharides from Auricularia auricula (Huaier) in adjuvant anti-gastrointestinal cancer therapy: a systematic review and network meta-analysis. *Pharmacol Res*. 2018;132:80–89. doi:10.1016/j.phrs.2018.04.010
15. Luo S, Hu H. Huaier granule prolongs overall survival after curative resection of hepatocarcinoma carcinoma: a propensity score analysis. *J Ethnopharmacol*. 2023;301:115774. doi:10.1016/j.jep.2022.115774
16. Wang Z, Yu XL, Zhang J, et al. Huaier granule prevents the recurrence of early-stage hepatocellular carcinoma after thermal ablation: a cohort study. *J Ethnopharmacol*. 2021;281:114539. doi:10.1016/j.jep.2021.114539
17. Bruix J, Takayama T, Mazzaferro V, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2015;16(13):1344–1354. doi:10.1016/S1470-2045(15)00198-9
18. Dai MG, Liu SY, Lu WF, Liang L, Ye B. Survival benefits from adjuvant lenvatinib for patients with hepatocellular carcinoma and microvascular invasion after curative hepatectomy. *Clin Med Insights Oncol*. 2023;17:11795549231180351. doi:10.1177/11795549231180351
19. Bai S, Hu L, Liu J, Sun M, Sun Y, Xue F. Prognostic nomograms combined adjuvant lenvatinib for Hepatitis B virus-related hepatocellular carcinoma with microvascular invasion after radical resection. *Front Oncol*. 2022;12:919824. doi:10.3389/fonc.2022.919824
20. Rodríguez-Perálvarez M, Luong TV, Andreana L, Meyer T, Dhillon AP, Burroughs AK. A systematic review of microvascular invasion in hepatocellular carcinoma: diagnostic and prognostic variability. *Ann Surg Oncol*. 2013;20(1):325–339. doi:10.1245/s10434-012-2513-1
21. Shibuya M. Vascular endothelial growth factor and its receptor system: physiological functions in angiogenesis and pathological roles in various diseases. *J Biochem*. 2013;153(1):13–19.

22. Wang X, Zhang N, Huo Q, Yang Q. Anti-angiogenic and antitumor activities of Huaier aqueous extract. *Oncol Rep*. 2012;28(4):1167–1175. doi:10.3892/or.2012.1961
23. Xiangdong H, Hai S, Zhongye H, Zhiqiang H, Zuohong M, Xibo F. Analysis of curative effect of huaier granule combined with transcatheter arterial chemoembolization following radical resection of primary hepatocellular carcinoma with microvascular invasion. *Chin J Bases Clin Gen Surg*. 2016;23(8):982–986.
24. Azam M, Hudgi A, Uy PP, Makhija J, Yap JEL. Safety of endoscopy in patients undergoing treatments with antiangiogenic agents: a 5-year retrospective review. *World J Gastrointest Endosc*. 2022;14(7):416–423. doi:10.4253/wjge.v14.i7.416
25. Bingqing D, Menglin H, Junyong C, Hang L, Zili S, Xiaodong S. Efficacy of Huai'er granules plus lenvatinib in treatment of advanced primary hepatic carcinoma. *Acad J Guangzhou Med College*. 2022;50(5):62–68.