Original Article

Huaier granule improves liver inflammation and fibrosis and prevents recurrence in hepatitis B virus related hepatocellular carcinoma

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Background: There is basic research suggesting that Huaier granule can inhibit liver cirrhosis and hepatocellular carcinoma (HCC), but this conclusion has not been clinically verified. We analyzed the distant cancer tissue of two groups of hepatitis B virus (HBV) related HCC with/without Huaier granule, to clarify the effect of Huaier granule on liver inflammation, liver fibrosis, and postoperative recurrence.

Methods: We collected clinicopathological data of HCC patients who received two surgery procedures at Mengchao Hepatobiliary Hospital of Fujian Medical University in China from January 2014 to December 2020. Patients according to taking/not taking Huaier granule after the first hepatectomy were divided into two groups, 51 patients with Huaier granule for more than 6 months after operation (Group A); 56 patients without Huaier granule (Group B). The effects on liver inflammation, fibrosis grade, and postoperative recurrence were compared between two groups.

Results: The results showed that liver inflammation improved significantly in the Group A [19 (37.3%) cases improved, 31 (60.8%) cases remained unchanged, and 1 (2.0%) case deteriorated] was significantly more than that in the Group B [7 (12.5%) cases improved, 32 (57.1%) cases remained unchanged, and 17 (30.4%) cases deteriorated] (P<0.001). The liver fibrosis in the Group A [17 (33.3%) cases improved, 32 (62.7%) cases remained unchanged, and 2 (3.9%) cases deteriorated] was significantly improved in the Group B [5 (8.9%) cases improved, 45 (80.4%) cases remained unchanged, and 6 (10.7%) cases deteriorated] (P=0.005). The recurrence interval (27.0±21.2 months) in the Group A was significantly longer than that in the Group B (19.0±14.2 months) (P=0.026).

Conclusions: Huaier granule can improve liver inflammation, fibrosis, and liver function and prolong the time to recurrence in HBV-related HCC. Given the high rate of postoperative recurrence and poor prognosis of HBV-related HCC, our findings may have useful clinical significance in the prevention of tumor recurrence in these patients.

Keywords: Hepatocellular carcinoma (HCC); Huaier granule; liver inflammation; liver fibrosis; recurrence

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Introduction

Hepatocellular carcinoma (HCC) ranks fifth in terms of global incidence and it is the third leading cause of death worldwide (1). In China, 90% of HCC patients are hepatitis B virus (HBV) infection, and with approximately 450,000 new cases of HCC annually, accounting for more than 50% of the new cases of HCC worldwide (2). HCC has become the second leading cause of death among cancer patients in China, with approximately 130,000 deaths each year (2). HBV and liver fibrosis are closely related to the development of HCC and postoperative recurrence, especially late recurrence (3,4).

Hepatic resection, ablation, chemotherapy, and liver transplantation are the main curative treatment options for patients with HCC (5-8). However, the high incidence of postoperative recurrence limits the efficacy of hepatic resection. Clinical practice shows that traditional Chinese medicine (TCM) plays an active role in improving clinical symptoms, enhancing the body's immunity, delaying tumor growth, alleviating adverse effects, and improving patients' life quality in HCC patients (9,10). At present, TCM has become an integral part of comprehensive treatment, more and more medical professionals have gradually agreed with its unique advantages, and tend to implement combination therapies in the treatment of HCC (11,12). To date, guidelines for diagnosis and treatment of oncology with TCM are developed as per international standards and are consistent with modern clinical practice (13,14).

Huaier is a kind of higher fungal fruiting body parasitic on old Sophora japonica. Huaier granule contains over 10 minerals and a diversity of organic ingredients. It has been widely used in traditional Chinese Medicine for nearly 1,600 years (15). In recent years, Huaier granule approved by the Chinese State Food and Drug Administration (SFDA) can be used alone or in combination with other drugs for the treatment of leukemia, osteosarcoma, malignant lymphoma cancer, breast cancer, lung cancer, rectal cancer, HCC, stomach cancer, colon cancer, and pancreatic cancer (16). Huaier granule can promote tumor cell apoptosis and enhance the immunity of the body (17). A recent multicenter, randomized, phase 3 clinical trial showed that Huaier granule significantly improved the tumor-free survival time and reduced the incidence of extrahepatic metastases after hepatectomy of HCC (18).

In liver cirrhosis, reversal of cirrhosis is difficult. Recently, an animal experiment found that Huaier granule had a strong inhibitory effect on cirrhosis and development of HCC, and the efficacy was closely correlated with the course of treatment (16). Therefore, Huaier granule may reduce post-operative relapse by inhibiting liver inflammation and fibrosis. However, this conclusion has not been clinically verified.

Therefore, we analyzed the distant cancerous tissues of HBV-related HCC patients who were/were not taking Huaier granule. To clarify the effect of Huaier granule on liver inflammation, liver fibrosis, and recurrence after hepatectomy in these patients. We present this article in accordance with the MDAR reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1347/rc).

Highlight box

Key findings

- Huaier granule can improve liver inflammation, fibrosis, and liver function and prolong the time to recurrence in hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC).

What is known and what is new?

- There is basic research suggesting that Huaier granule can inhibit liver cirrhosis and HCC, but this conclusion has not been clinically verified.
- The results showed that liver inflammation improved significantly in the Group A [19 (37.3%) cases improved, 31 (60.8%) cases remained unchanged, and one (2.0%) case deteriorated] was significantly more than that in the Group B [7 (12.5%) cases improved, 32 (57.1%) cases remained unchanged, and 17 (30.4%) cases deteriorated] (P<0.001). The liver fibrosis in the Group A [17 (33.3%) cases improved, 32 (62.7%) cases remained unchanged, and 2 (3.9%) cases deteriorated] was significantly improved in the Group B [5 (8.9%) cases improved, 45 (80.4%) cases remained unchanged, and 6 (10.7%) cases deteriorated] (P=0.005). The recurrence interval (27.0±21.2 months) in the Group A was significantly longer than that in the Group B (19.0±14.2 months) (P=0.026).

What is the implication, and what should change now?

- Given the high rate of postoperative recurrence and poor prognosis of HBV-related HCC, our findings may have useful clinical significance in the prevention of tumor recurrence in these patients.

Methods

Patient eligibility

Clinicopathological data of HCC patients who received 2 surgery procedures at Mengchao Hepatobiliary Hospital of Fujian Medical University in China from January 2014 to December 2020 were initially collected. The study was conducted in accordance with the Declaration of Helsinki

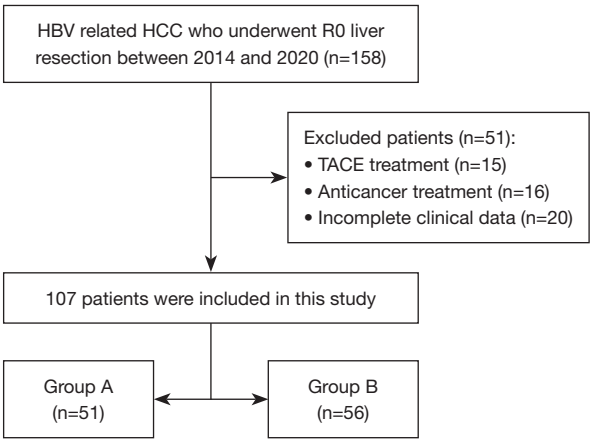


Figure 1 The flow chart of the study. Group A: with Huaier granual; Group B: without Huaier ganual. HBV, hepatitis B virus; HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization.

(as revised in 2013). The study was approved by the institutional ethics committee of Mengchao Hepatobiliary Hospital of Fujian Medical University (No. 2022_020_01). Informed consent requirement was waived due to the fact that this study did not involve personal privacy nor commercial interests and patient data were confidential.

Eligibility criteria included (I) pathologically confirmed HCC; (II) with combined hepatitis B; (III) received standardized anti-HBV treatment; (IV) with residual distant cancerous tissue in both surgeries.

Exclusion criteria included (I) patients with incomplete clinical data; (II) with postoperative transcatheter arterial chemoembolization (TACE); (III) patients who received other anti-tumor treatments.

Study design

Patients according to taking or not taking Huaier granule after the first hepatectomy were divided into two groups: patients in the Huaier granule treatment group started oral administration of Huaier granule after a week of hepatectomy and kept the administration for over 6 months (20 g/time, 3 times a day, Group A); patients in the control group did not take Huaier granule (Group B).

Measurements

Baseline clinical variables for the included subjects included gender, age, liver function, alpha-fetoprotein (AFP), hepatitis B virus deoxyribonucleic acid (HBV-DNA) load, tumor size, tumor number, Barcelona Clinic Liver Cancer (BCLC) stage, recurrence interval, liver inflammation grade, liver fibrosis grade. All pathological specimens were independently reassessed by two pathologists. Modified Scheuer scoring system was used for liver inflammation and fibrosis. According to the changes in inflammation and fibrosis grading of distant cancerous tissues at the time of the first and second surgery, three conditions were defined: improved, unchanged, and deteriorated.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) and compared by *t*-tests, and categorical variables were expressed as n (%). Differences in categorical variables were compared with the Chi-squared test or Fisher's exact test. All statistical tests were two-tailed, and $P<0.05$ was considered statistically significant. All statistical analyses were performed using R version 3.5.2 (http://www.r-project.org/).

Results

Demographics

Between January 2014 and December 2020, 158 patients with HCC treated with two surgeries from Mengchao Hepatobiliary Hospital of Fujian Medical University were included.15 cases were excluded from postoperative TACE, 16 cases were excluded from receiving other antitumor therapy, and 20 cases were excluded from incomplete clinical data. A total of 107 cases were eligible for enrollment in this study (*Figure 1*). Among them, 51 cases who took Huaier granule for more than six months after surgery were set up as treatment group (Group A, 51 cases); 56 cases who did not take Huaier granule were set up as control group (Group B, 56 cases).

Baseline characteristics of study patients at first surgery

Table 1 shows the baseline characteristics of patients who received their first surgery. The mean age of these patients was 58.1±11.6 years; 92 cases (86%) were males; the albumin was 39.7±5.49 g/L, total bilirubin 17.8±8.83 μmol/L, alanine aminotransferase (ALT) 50.1±68.1 U/L and aspartate aminotransferase (AST) 45.2±44.8 U/L; the AFP level was ≥400 ng/mL in 38 patients (35.5%), HBV-DNA ≥10,000 IU/L in 42 patients (39.3%); mean tumor

Table 1 Comparison of baseline characteristics of patients at first surgery between two groups

Variables	Overall (n=107)	Group A (n=51)	Group B (n=56)	P value
Age, years	58.1 (11.6)	58.0 (11.9)	58.2 (11.3)	0.950
Gender				0.996
Female	15 (14.0)	7 (13.7)	8 (14.3)	
Male	92 (86.0)	44 (86.3)	48 (85.7)	
ALB, g/L	39.7 (5.49)	40.3 (5.29)	39.2 (5.67)	0.302
TBIL, μmol/L	17.8 (8.83)	18.2 (8.04)	17.5 (9.55)	0.686
ALT, U/L	50.1 (68.1)	56.3 (87.4)	44.4 (44.0)	0.381
AST, U/L	45.2 (44.8)	48.2 (58.5)	42.6 (27.1)	0.537
AFP				0.334
<400 ng/mL	69 (64.5)	30 (58.8)	39 (69.6)	
≥400 ng/mL	38 (35.5)	21 (41.2)	17 (30.4)	
HBV-DNA				0.557
<10,000 IU/L	65 (60.7)	29 (56.9)	36 (64.3)	
≥10,000 IU/L	42 (39.3)	22 (43.1)	20 (35.7)	
Tumor size, cm	4.53 (3.34)	4.73 (3.10)	4.34 (3.57)	0.543
Tumor number				0.451
Solitary	92 (86.0)	45 (88.2)	47 (83.9)	
Multiple	15 (14.0)	6 (11.8)	9 (16.1)	
BCLC stage				0.729
0/A	88 (82.2)	43 (84.3)	45 (80.4)	
B	11 (10.3)	4 (7.8)	7 (12.5)	
C	8 (7.5)	4 (7.8)	4 (7.1)	

Categorical variables are presented as number (percentage). Mean (standard deviation) presented for distributed continuous variables. Group A: with Huaier granual; Group B: without Huaier ganual. ALB, albumin; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, alpha-fetoprotein; HBV-DNA, hepatitis B virus deoxyribonucleic acid; BCLC, Barcelona Clinic Liver Cancer.

size was 4.53±3.34 cm; there were 92 (86%) cases in with single-tumor, 88 (82.2%) in BCLC stage 0/A, 11 (10.3%) in BCLC stage B and 8 (7.5%) in BCLC stage C. No significant differences were found between the two groups in age, gender, liver function, AFP, HBV-DNA, tumor size and number, BCLC stage at first surgery.

Baseline characteristics of study patients at the second surgery

Table 2 shows the liver function of patients who received second surgery. The albumin was 39.1±7.07 g/L, total bilirubin 18.4±12.5 μmol/L, ALT 33.7±42.7 U/L and AST 33.6±35.8 U/L; the AFP level was ≥400 ng/mL in 20 patients (18.7%), HBV-DNA ≥10,000 IU/L in one patient (0.9%). The albumin levels at the second operation of HCC patients in the Group A were significantly higher than those in the Group B (P=0.038).

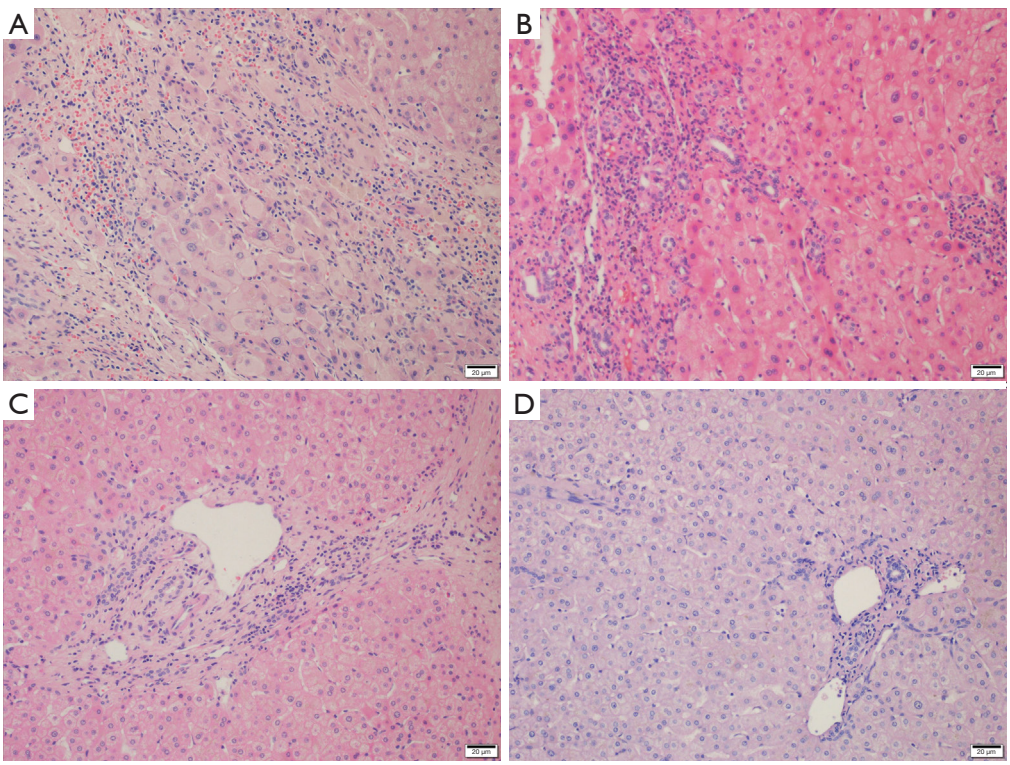
The effect of Huaier granule on hepatitis, liver fibrosis, and recurrence time

Figure 2 shows the hematoxylin-eosin (HE) stained pictures of the hepatic inflammation grading of distant cancer tissues from 3 patients. *Figure 2A,2B* showed the liver inflammation grades in the distant cancer tissue of the first

Table 2 Comparison of baseline characteristics of patients at second surgery between two groups

Variables	Overall (n=107)	Group A (n=51)	Group B (n=56)	P value
ALB, g/L	39.1 (7.07)	40.6 (6.00)	37.8 (7.73)	0.038
TBIL, μmol/L	18.4 (12.5)	16.6 (5.74)	20.0 (16.4)	0.153
ALT, U/L	33.7 (42.7)	27.6 (14.1)	39.2 (57.2)	0.149
AST, U/L	33.6 (35.8)	29.3 (11.5)	37.6 (48.1)	0.217
AFP				0.987
<400 ng/mL	87 (81.3)	42 (82.4)	45 (80.4)	
≥400 ng/mL	20 (18.7)	9 (17.6)	11 (19.6)	
HBV-DNA				0.963
<10,000 IU/L	106 (99.1)	50 (98.0)	56 (100.0)	
≥10,000 IU/L	1 (0.9)	1 (2.0)	0 (0)	

Categorical variables are presented as no. (%). Mean (standard deviation) presented for distributed continuous variables. Group A: with Huaier granual; Group B: without Huaier ganual. ALB, albumin; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, alpha-fetoprotein; HBV-DNA, hepatitis B virus deoxyribonucleic acid.



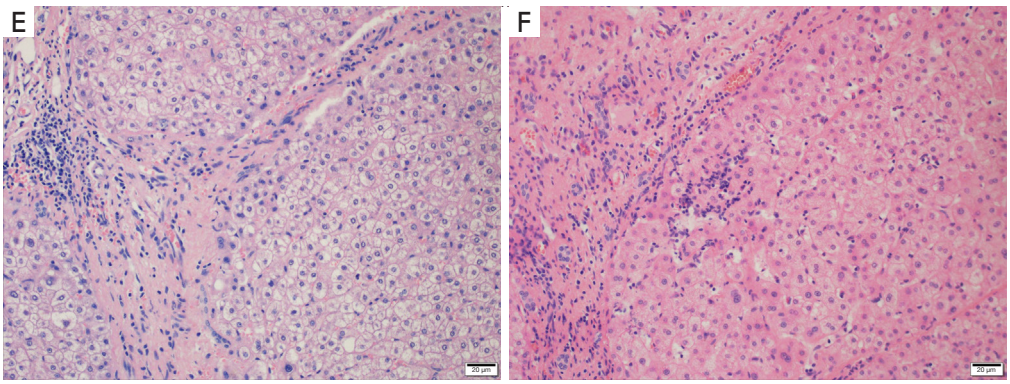


Figure 2 Hematoxylin-eosin staining (×100) of liver inflammation grade in distant cancer tissues of 3 patients. (A,B) Liver inflammation grades (G2, G1) in the distant cancer tissue of the first and the second operations of case 1; (C,D) liver inflammation grades (G2, G2) in the distant cancer tissue of the first and the second operations of case 2; (E,F) liver inflammation grades (G1, G2) in the distant cancer tissue of the first and the second operations of case 3).

Table 3 Comparison of liver inflammation, liver cirrhosis, and recurrence time interval between two groups of patients

Variables	Overall (n=107)	Group A (n=51)	Group B (n=56)	P value
Liver inflammation				<0.001
Improved	26 (24.3)	19 (37.3)	7 (12.5)	
Unchanged	63 (58.9)	31 (60.8)	32 (57.1)	
Deteriorated	18 (16.8)	1 (2.0)	17 (30.4)	
Liver cirrhosis				0.005
Improved	22 (20.6)	17 (33.3)	5 (8.9)	
Unchanged	77 (72.0)	32 (62.7)	45 (80.4)	
Deteriorated	8 (7.5)	2 (3.9)	6 (10.7)	
Recurrence interval, months	22.9 (18.2)	27.0 (21.2)	19.0 (14.2)	0.026

Categorical variables are presented as number (percentage). Mean (standard deviation) presented for distributed continuous variables. Group A: with Huaier granual; Group B: without Huaier ganual.

and the second operations of case 1, showing improvement in liver inflammation in this patient (G2 becomes G1). *Figure 2C,2D* showed the liver inflammation grades in the distant cancer tissue of the first and the second operations of case 2, showing no change in liver inflammation of this patient. *Figure 2E,2F* showed the liver inflammation grades in the distant cancer tissue of the first and the second operations of case 3, showing worse liver inflammation in this patient (G1 becomes G2). The results showed that the liver inflammation improved significantly in the Group A [19 (37.3%) cases improved, 31 (60.8%) cases remained unchanged, and 1 (2.0%) case deteriorated] was significantly more than that in the Group B [7 (12.5%) cases improved, 32 (57.1%) cases remained unchanged, and 17 (30.3%) cases deteriorated] (P<0.001) (*Table 3*).

Figure 3 shows the Masson-stained pictures of the hepatic inflammation grading of distant cancer tissues from 3 patients. *Figure 3A,3B* showed the liver fibrosis grades in the distant cancer tissue of the first and the second operations of case 1, showing improvement in liver fibrosis in this patient (S4 becomes S3). *Figure 3C,3D* showed the liver fibrosis grades in the distant cancer tissue of the first and the second operations of case 2, showing no change in liver fibrosis of this patient. *Figure 3E,3F* showed the liver fibrosis grades in the distant cancer tissue of the first and the second operations of case 3, showing worse liver

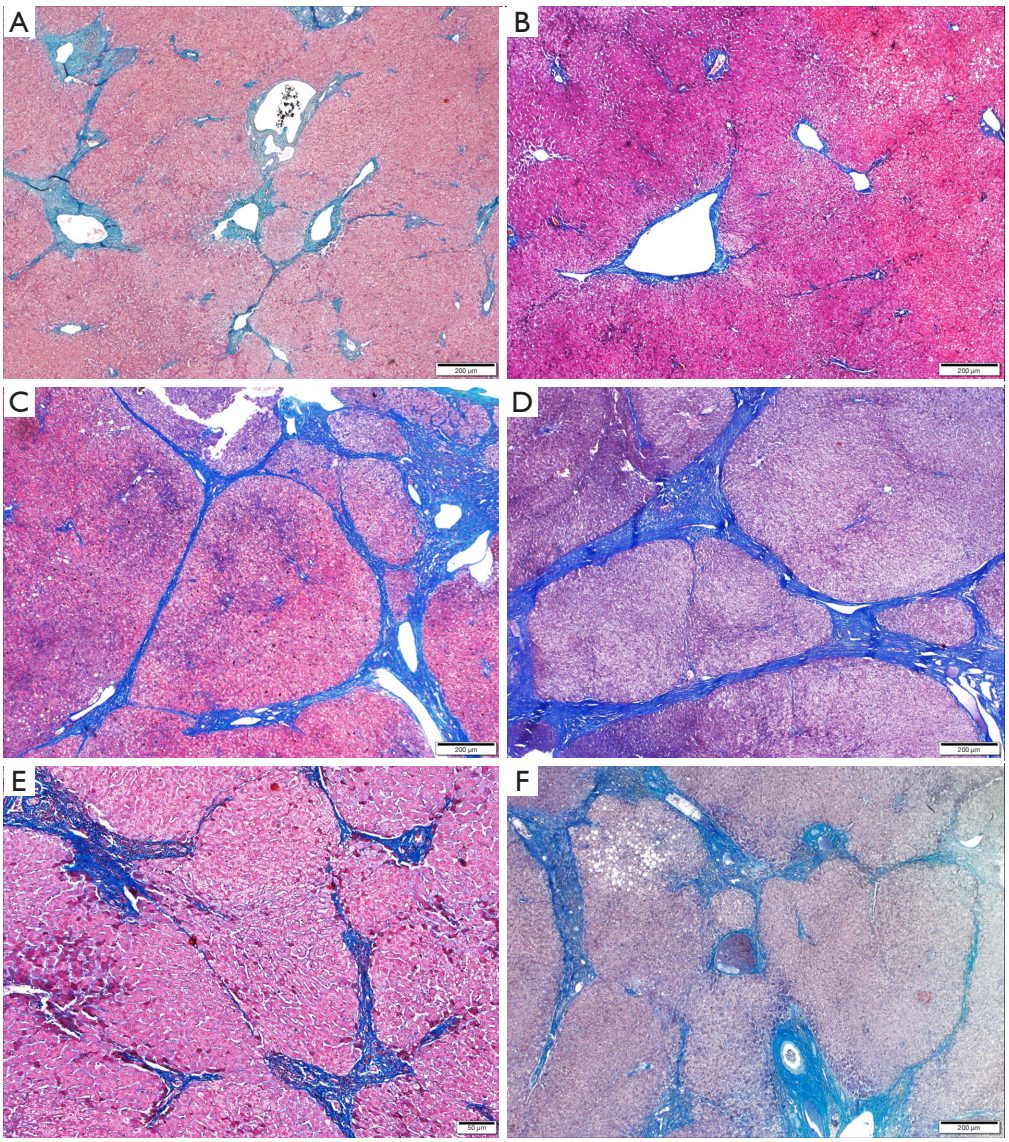


Figure 3 Masson stain (×10) of liver inflammation grade in distant cancer tissues of 3 patients. (A,B) Liver fibrosis grades (S4, S3) in the distant cancer tissue of the first and the second operations of case 1; (C,D) liver fibrosis grades (S4, S4) in the distant cancer tissue of the first and the second operations of case 2; (E,F) liver fibrosis grades (S2, S3) in the distant cancer tissue of the first and the second operations of case 3).

fibrosis in this patient (S2 becomes S3). The liver fibrosis in the Group A [17 (33.4%) cases improved, 32 (62.7%) cases remained unchanged, and 2 (3.9%) cases deteriorated] was significantly improved than that in the Group B [5 (8.9%) cases improved, 45 (80.4%) cases remained unchanged, and 6 (10.7%) cases deteriorated] (P=0.005) (*Table 3*).

In addition, the recurrence interval (27.0±21.2 months) in the Group A was significantly longer than that in the Group B (19.0±14.2 months) (P=0.026). The above results indicated that Huaier granule can improve liver inflammation and liver fibrosis and prolong the recurrence time of HCC after surgery in HBV-related HCC.

Discussion

In China, 90% of HCC patients are HBV-related HCC.

The incidence of HCC is particularly high in the Chinese population due to the high prevalence of HBV infection in China (19). HBV and liver cirrhosis are closely related to the development of HCC and its recurrence after surgery (20,21).

The incidence rate of HCC in patients with cirrhosis is as high as 50–85%. Liver cirrhosis is an important contributing factor for the development of HCC (22). Huaier granule has the effect of strengthening and consolidating body resistance, promoting blood circulation, and removing blood stasis consolidating body resistance (23). A study has shown that it can promote tumor cell apoptosis, regulate body immunity, reverse drug resistance, and inhibit angiogenesis, etc. (24). It is used in the treatment of HCC, stomach cancer, breast cancer, and other cancers (16).

Basic experimental study has also shown that Huaier granule have the effect of improving liver cirrhosis (16). Chen *et al.* found Huaier presented a strong inhibitory effect on cirrhosis and HCC and its efficacy was closely related to the duration of treatments (16). However, this result has not been clinically validated. The effect of Huaier granule on liver inflammation and cirrhosis has not been reported. This study is the first to clinically demonstrate that Huaier granule can improve liver inflammation and liver function and reverse liver fibrosis/cirrhosis in HBV-related HCC.

A randomized, controlled, and multicenter clinical study by Chen *et al.* confirmed Huaier granule had an anti-recurrence effect after radical resection of HCC (18). Currently, it is commonly believed that postoperative recurrence of HCC is divided into early recurrence (less than 2 years) and late recurrence (more than 2 years) (3,4,25). Early recurrence is associated with residual tumor (seed theory) and late recurrence is mainly related to the patient's underlying liver pathology (soil theory) (26,27). The results of this study showed that taking Huaier granule can significantly prolong the postoperative recurrence time of patients with HBV-related HCC, with an average recurrence time of 27 months. This suggests that Huaier granule have an anti-HCC recurrence effect, and the effect is mainly reflected in the anti-late recurrence.

Our study has several limitations. Firstly, a retrospective study is inherently biased. Therefore, in future experiments, expanding the sample size and future prospective randomized studies are required to confirm the findings. Secondly, inhibition of the transformation of liver fibrosis/cirrhosis to HCC may be one of the mechanisms. However, the molecular mechanisms need to be further investigated.

Conclusions

Huaier granule can improve liver inflammation, fibrosis, and liver function and prolong the time to recurrence in HBV-related HCC. Given the high rate of postoperative recurrence and poor prognosis of HBV-related HCC, our findings may have useful clinical significance in the prevention of tumor recurrence in these patients.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1347/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1347/dss

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1347/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1347/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committee of Mengchao Hepatobiliary Hospital of Fujian Medical University (No. 2022_020_01). Informed consent requirement was waived due to the fact that this study did not involve personal privacy nor

commercial interests and patient data were confidential.

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