Postprint of a Randomized Controlled Trial of Qizhu Huaji Formula for Patients with Precancerous Lesions of Hepatocellular Carcinoma

Authors: Ning Lin, Sun Jianguang, Sun Jianguang

Date: 2022-12-23T00:00:00+00:00

Abstract

Objective To observe the clinical efficacy and safety of Qizhu Huaji Formula in treating precancerous lesions of hepatocellular carcinoma (pattern of liver depression and spleen deficiency with intermingled phlegm and stasis). Methods Sixty-four patients meeting inclusion criteria were randomly divided into observation group (34 cases) and control group (30 cases). The control group received conventional treatment including etiological treatment and hepatoprotective therapy, while the observation group received conventional treatment combined with Qizhu Huaji Formula. The treatment course was 48 weeks, followed by 48 weeks of follow-up after discontinuation. Changes in symptoms and signs, liver function, tumor marker indicators, lesion nodule long diameter, etc. were observed before and after treatment, and the incidence of liver cancer and complications were observed during the treatment and follow-up periods. Results Compared with before treatment, TCM syndrome scores, liver function indicators including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), and gamma-glutamyl transpeptidase (GGT) values, and alpha-fetoprotein heterodimer (AFP-L3) ratio were all lower in both groups ($P<0.05$). In the observation group after treatment, AFP-L3 ratio and des-gamma-carboxy prothrombin (DCP) level were also lower than before treatment, and lesion long diameter decreased compared with before treatment ($P<0.01$). Inter-group comparison showed that TCM syndrome scores, AST, and alkaline phosphatase (ALP) values in the observation group were lower than those in the control group, while serum albumin (ALB) value was higher than that in the control group ($P<0.05$). After the treatment cycle, the total improvement rate of lesions in the observation group was 35.29% and the total stability rate was 50%, which were better than those in the control group (20%, 43.33%). After the follow-up cycle, the liver cancer incidence in the observation group (8.82%) was lower than that in the control group (16.67%),

and the complication incidence (8.82%) was also lower than that in the control group (30%) (P<0.05). During the entire study period, 2 patients in the observation group experienced mild adverse reactions, and 3 patients in the control group experienced mild adverse reactions; no abnormal safety indicators occurred in either group. Conclusion Qizhu Huaji Formula for precancerous lesions of hepatocellular carcinoma (pattern of liver depression and spleen deficiency with intermingled phlegm and stasis) demonstrates good clinical efficacy and safety in improving TCM syndromes, improving liver function, reducing lesion nodules, decreasing long-term liver cancer incidence, and reducing cirrhosis complications.

Full Text

Preamble

Qizhuhuaji Formula in the Treatment of Patients with Hepatocellular Carcinoma Precancerous Lesions: A Randomized Controlled Study

Authors: NING Lin, SUN Jianguang*
Affiliation: The First Clinical Medical College, Shandong University of Traditional Chinese Medicine, Jinan 250014, China
Corresponding Author: SUN Jianguang, Professor, Doctoral Supervisor; E-mail: 15275319001@163.com

Abstract

Objective: To observe the clinical efficacy and safety of Qizhuhuaji Formula in treating hepatocellular carcinoma (HCC) precancerous lesions (characterized by liver depression and spleen deficiency with phlegm-blood stasis syndrome). **Methods:** Sixty-four eligible patients were randomly assigned to either the observation group (n=34) or the control group (n=30). The control group received conventional treatment including etiological therapy and hepatoprotective therapy, while the observation group received conventional treatment combined with Qizhuhuaji Formula. The treatment course was 48 weeks, followed by a 48-week post-treatment follow-up period. Changes in symptoms, signs, liver function, tumor markers, and lesion nodule dimensions were observed before and after treatment, along with the incidence of liver cancer and complications during both the treatment and follow-up periods. **Results:** Compared with baseline, both groups showed significant reductions in Traditional Chinese Medicine (TCM) syndrome scores, liver function parameters (ALT, AST, TBIL, GGT), and AFP-L3 ratio (P<0.05). The observation group additionally demonstrated decreased AFP-L3 ratio and DCP levels post-treatment, with significant reduction in lesion diameter (P<0.01). Inter-group comparison revealed that the observation group had lower TCM syndrome scores, AST, and ALP values, and higher ALB values compared to the control group (P<0.05). After the treatment period, the observation group achieved a total lesion improvement rate of 35.29% and stability rate of 50%, superior to the control group's 20% and 43.33%, respectively. Following the follow-up period, the observation group's

liver cancer incidence (8.82%) was lower than the control group's (16.67%), with complication rates also lower (8.82% vs. 30%) ($P<0.05$). Throughout the study, 2 patients in the observation group and 3 in the control group experienced mild adverse reactions, with no abnormal safety indicators in either group. **Conclusion:** Qizhuhuaji Formula demonstrates favorable clinical efficacy and safety in treating HCC precancerous lesions (liver depression and spleen deficiency, phlegm-blood stasis syndrome), effectively improving TCM syndromes, liver function, reducing lesion size, decreasing long-term liver cancer incidence, and reducing cirrhosis complications.

Keywords: Qizhuhuaji Formula; Hepatocellular Carcinoma Precancerous Lesions; Liver Depression and Spleen Deficiency, Phlegm-Blood Stasis Syndrome; Clinical Observation

---

Introduction

Hepatocellular carcinoma (HCC) ranks as the fourth most common malignant tumor and the second leading cause of cancer-related mortality in China, with a 5-year overall survival rate below 15%. Approximately 400,000 deaths annually are attributed to liver cancer in China, accounting for about 51% of global liver cancer mortality, representing a severe public health challenge. Current HCC management faces issues including late diagnosis, rapid disease progression, suboptimal treatment outcomes, and high recurrence rates. Consequently, shifting the focus of HCC prevention and treatment upstream has gained widespread recognition, with early diagnosis and timely intervention at the precancerous lesion stage representing a critical strategy to block chronic liver disease progression and reduce HCC incidence.

Precancerous lesions occur during the malignant transformation from chronic liver disease to HCC. High-grade dysplastic nodules (HGDN) carry a 30-40% risk of malignant transformation within 24 months. While Western medicine's understanding of HCC precancerous lesions continues to deepen, with diagnostic methods encompassing pathology, imaging, and serology, treatment remains primarily limited to surveillance monitoring, with local ablation or surgical resection recommended when necessary. However, large-scale prospective clinical studies are still needed to address questions regarding optimal timing of surgical intervention and potential overtreatment.

Chinese medicine, grounded in the "preventive treatment" philosophy and guided by the principle of "strengthening vital qi while dispelling pathogenic factors," offers holistic treatment with flexible prescriptions, demonstrating irreplaceable advantages. Existing literature reports that single herbal extracts, herbal formulas, and acupuncture all show promising efficacy. Through years of clinical practice, our research team has identified "liver depression and spleen deficiency with phlegm-blood stasis" as the key pathogenesis, with "soothing the liver, strengthening the spleen, and resolving stasis to detoxify" as an effective therapeutic approach. Based on preliminary research and clinical

experience, we optimized the prescription to create Qizhuhuaji Formula for HCC precancerous lesions, which has achieved satisfactory clinical results. This randomized controlled trial investigates the efficacy and safety of Qizhuhuaji Formula in improving symptoms, reducing lesions, decreasing long-term liver cancer incidence, and reducing cirrhosis complications, aiming to provide theoretical and practical foundations for Chinese medicine treatment of HCC precancerous lesions.

1.1.1 Western Diagnostic Criteria

Western diagnostic criteria were established according to the *Multidisciplinary Expert Consensus on the Diagnosis and Treatment of Hepatocellular Carcinoma Precancerous Lesions (2020 Edition)*: lesions occurring in the context of chronic hepatitis B or other liver diseases that meet pathological diagnostic criteria, or simultaneously meet imaging and serological criteria when pathological diagnosis is unavailable.

(1) Imaging Diagnosis: Includes regenerative nodules (RN), low-grade dysplastic nodules (LGDN), and high-grade dysplastic nodules (HGDN).
Note: All enrolled cases in this study were confirmed by contrast-enhanced CT or MRI, with liver-specific contrast agent gadoxetic acid-enhanced MRI (EOB-MRI) performed when necessary.

(2) Serological Diagnosis:
Alpha-fetoprotein (AFP), particularly elevated AFP-L3;
Elevated des-γ-carboxy-prothrombin (DCP);
Abnormal glypican-3 (GPC-3);
Abnormal osteopontin (OPN).
Note: Multiple combined tests are typically required for serological diagnosis. This study primarily observed three tumor markers: AFP, AFP-L3, and DCP.

(3) Pathological Diagnosis: Dysplastic foci (DF) and dysplastic nodules (DN) identified microscopically.

1.1.2 TCM Syndrome Differentiation Criteria

Based on the *Standardized Diagnostic and Treatment Guidelines for Primary Liver Cancer (2019 Edition)* and *Diagnostics of Traditional Chinese Medicine* textbooks, the diagnostic criteria for liver depression and spleen deficiency with phlegm-blood stasis syndrome were established as follows:

Primary Symptoms:
Right hypochondriac discomfort or distending pain;
Fatigue and lassitude.

Secondary Symptoms:
Epigastric fullness and poor appetite;

Heavy sensation in limbs;
Loose stools;
Lower limb edema;
Hypochondriac mass;
Sallow or dull complexion.

Tongue and Pulse:
Dark or tooth-marked tongue with thin white or white greasy coating; deep wiry or choppy pulse.

Syndrome Confirmation: Diagnosis requires 2 primary symptoms + 2 secondary symptoms, with reference to tongue and pulse findings.

1.2 Inclusion Criteria

(1) Meet Western diagnostic criteria for the disease;

(2) Imaging diagnosis of RN or LGDN;

(3) Imaging diagnosis of HGDN with refusal of local ablation or surgical resection;

(4) Chronic HBV infection with complete virological response after antiviral therapy;

(5) Meet TCM syndrome differentiation criteria for liver depression and spleen deficiency with phlegm-blood stasis;

(6) No prior use of other medications for this condition;

(7) Provided informed consent and voluntary participation with compliance.

1.3 Exclusion Criteria

(1) Failure to meet inclusion criteria;

(2) Comorbid primary diseases of heart, brain, kidney, lung, blood, or psychiatric disorders;

(3) Confirmed HCC or HGDN patients willing to undergo local ablation/surgical resection;

(4) Severe hepatitis or decompensated cirrhosis;

(5) Pregnant or lactating women;

(6) Self-administration of other medications during the study;

(7) Poor compliance or unwillingness to cooperate;

(8) History of allergy to similar herbal components.

1.4 Termination Criteria

For cases progressing to HCC during treatment or follow-up, the study terminated upon clinical or pathological confirmation of HCC. For participants withdrawing early, the last follow-up date before withdrawal was recorded as the study termination date.

Patient Enrollment

Study participants were recruited from the liver disease outpatient clinics of Shandong University of Traditional Chinese Medicine Affiliated Hospital, Weihai Traditional Chinese Medicine Hospital, and Tai'an Traditional Chinese Medicine Hospital between October 2019 and March 2020. A total of 67 patients with chronic hepatitis B background met the inclusion criteria and were randomly assigned to the observation group (n=36) or control group (n=31). During the study, 2 cases were lost to follow-up in the observation group and 1 case in the control group withdrew due to other major diseases, leaving 64 completed cases (observation group: n=34; control group: n=30). The cohort included 49 males and 15 females, with 52 patients having post-hepatitis B cirrhosis. No statistically significant differences existed between groups in gender, age, cirrhosis history, family history of liver cancer, or alcohol consumption history.

2.2 Treatment Methods

Control Group:
- Antiviral therapy: Entecavir capsules (Fujian Cosunter Pharmaceutical Co., Ltd.) 0.5 mg orally once daily, taken at least 2 hours before or after meals.
- Anti-inflammatory hepatoprotective therapy: For patients with abnormal serum liver enzymes, silybin meglumine tablets (Jiangsu Zhongxing Pharmaceutical Co., Ltd.) 150 mg three times daily, and tiānqíng gānpíng (Chia Tai Tianqing Pharmaceutical Co.) 150 mg three times daily.

Observation Group:
In addition to conventional treatment, patients received the herbal formula Qizhuhuaji Formula:
Astragalus membranaceus (huángqí) 60g, *Atractylodes macrocephala* (báizhú) 20g, *Poria cocos* (fúlíng) 20g, stir-fried *Dioscorea opposita* (shānyào) 30g, stir-fried *Coix lacryma-jobi* (yìyǐrén) 30g, *Cyperus rotundus* (xiāngfù) 15g, *Curcuma aromatica* (yùjīn) 15g, *Fritillaria thunbergii* (zhèbèi) 9g, *Ostrea gigas* (mǔlì) 20g,

Verbena officinalis (mǎbiāncǎo) 20g, *Trionyx sinensis* (biējiǎ) 20g (decocted first), *Gallus gallus domesticus* (jīnèijīn) 20g, *Angelica sinensis* (dāngguī) 12g, *Curcuma zedoaria* (ézhú) 12g, *Scorpio* (quánxiē) 9g, *Scolopendra* (wúgōng) 3 pieces, *Paris polyphylla* (chónglóu) 9g, *Hedyotis diffusa* (báihuāshéshécǎo) 30g, and *Glycyrrhiza uralensis* (zhìgāncǎo) 6g.

Preparation: Trionyx sinensis was decocted first for 30 minutes, followed by addition of other herbs. All herbs were decocted twice and combined to 400 ml, taken warm 30 minutes after breakfast and dinner.

Both groups underwent contrast-enhanced CT, MRI, or EOB-MRI and serum tumor marker/liver function tests every three months. The treatment duration was 48 weeks, after which antiviral therapy continued with follow-up every 12 weeks until HCC development or 48 weeks of follow-up.

2.3.1 Efficacy Indicators

(1) **TCM Syndrome Improvement Index:** TCM syndrome scores collected through four diagnostic methods and quantified according to TCM syndrome grading scales.

(2) **Liver Function Indicators:** ALT, AST, TBIL, ALB, GGT, and ALP.

(3) **Tumor Markers:** AFP, AFP-L3, and DCP recorded before and after treatment.

(4) **Imaging Indicators:** Contrast-enhanced CT, MRI, or EOB-MRI results recorded before and after treatment.

All indicators were reassessed every three months, with at least one recording before treatment, after treatment, and at final follow-up. Liver cancer incidence and complication rates were documented for both groups.

2.3.2 Safety Indicators

Complete blood count, urinalysis, stool routine + occult blood, 12-lead ECG, renal function, and physical examination were performed at least once before and after treatment. Additionally, adverse event types, severity, and frequency were monitored throughout the treatment period.

2.4.1 Efficacy Evaluation Criteria

TCM Syndrome Efficacy Criteria:
- Cured: $ $95% reduction in syndrome score
- Markedly effective: $70\% \leq$ reduction $< 95\%$

- Effective: 30% ≤ reduction < 70%
- Ineffective: <30% reduction

Note: Reduction percentage = [(pre-treatment score - post-treatment score)/pre-treatment score] × 100%; Total effective rate = [(cured + markedly effective + effective cases)/total cases] × 100%. All symptoms were graded as none, mild, moderate, or severe.

Imaging Efficacy Criteria (based on RECIST guidelines):
- Cured: Disappearance of all lesions
- Remission: $ $30% reduction in longest diameter of baseline lesions
- Stable: Reduction not meeting "remission" criteria or unchanged
- Progression: Increase in longest diameter or appearance of new lesions

Note: Improvement rate = [(cured + remission cases)/total cases] × 100%; Stability rate = (stable cases/total cases) × 100%.

2.4.2 Safety Evaluation Criteria

Level I: Safe, no adverse reactions, normal safety indicators
Level II: Relatively safe, mild adverse reactions, normal safety indicators, can continue medication without intervention
Level III: Safety concerns, moderate adverse reactions, or mild abnormalities in safety indicators, can continue medication after management
Level IV: Trial discontinued due to adverse reactions, or significant abnormalities in safety indicators

---

2.5 Statistical Methods

Data were analyzed using SPSS 25.0. Categorical data were expressed as (n) and analyzed using chi-square or Fisher's exact test. Normally distributed continuous data were analyzed using t-tests and expressed as ($x \pm s$); non-normally distributed data used rank-sum tests and were expressed as M(P25, P75). Ranked data were analyzed using rank-sum tests. Statistical significance was defined as $P<0.05$.

3.2.1 TCM Syndrome Efficacy Evaluation

As shown in Tables 3 and 4, post-treatment syndrome scores decreased in both groups, with the observation group's scores significantly lower than the control group's. The TCM syndrome improvement effective rate was higher in the observation group (91.18% vs. 63.33%), with statistically significant differences ($P<0.05$). These results indicate that both treatments improved clinical symptoms, with the observation group showing superior TCM syndrome improvement.

Table 3. Comparison of TCM Syndrome Scores Before and After Treatment (x±s) | Group | Pre-treatment Score | Post-treatment Score | |——-|————————|————————-| | Observation | 11.47$±4.65|4.15±4.46#▽||*Control*|9.5±3.38|7.23±$5.84* |

Note: #P<0.01, P<0.05 vs. pre-treatment; P<0.05 vs. control group post-treatment.*

Table 4. Comparison of TCM Syndrome Efficacy Between Groups | Group | n | Effective Rate | |——-|—|————-| | Observation | 34 | 91.18% | | Control | 30 | 63.33% |

3.2.2 Liver Function Indicator Efficacy Evaluation

Tables 5 and 6 demonstrate that both groups showed significant reductions in ALT, AST, TBIL, and GGT, and increased ALB after treatment (P<0.05 or P<0.01). The observation group also showed significant reduction in ALP (P<0.01). Inter-group comparison revealed that post-treatment AST and ALP were lower, and ALB higher, in the observation group compared to controls (P<0.05), indicating Qizhuhuaji Formula's superior efficacy in improving liver function.

Table 5. Comparison of ALT, AST, and TBIL Before and After Treatment [M(P25, P75)] | Group | ALT (U/L) | AST (U/L) | TBIL (mol/L) | |——-|————|————|—————| | Observation (pre) | 32(23.75,45) | 30.5(25,45.5) | 18.45(15,27.35) | | Observation (post) | 25.5(19,36.25)# | 25(16.75,31)# | 15(13,23.25)# | | Control (pre) | 32.2(21.8,48.75) | 31(26,58.325) | 18.8(14.8,29.6) | | Control (post) | 29(21.25,43)# | 31(23,39.25)# | 17(13.75,23.575)# |

Note: #P<0.01 vs. pre-treatment; P<0.05, P>0.05 vs. control group post-treatment.

Table 6. Comparison of ALB, GGT, and ALP Before and After Treatment [M(P25, P75)] | Group | ALB (g/L) | GGT (U/L) | ALP (U/L) | |——-|————|————|————| | Observation (pre) | 38.75(32.85,43.55) | 37(27,66.6) | 70(57,90.25) | | Observation (post) | 42.5(39.025,45)# | 36.5(24.75,48.75)# | 55.5(43,81.25)# | | Control (pre) | 37.2(33.35,42.025) | 36(25.75,65.25) | 83(62.5,107.5) | | Control (post) | 38.6(35.8,43.05)# | 33.25(22.75,56.03)* | 77.75(57,103.5) |

Note: #P<0.01, P<0.05, P>0.05 vs. pre-treatment; P<0.05, P>0.05 vs. control group post-treatment.*

3.2.3 Tumor Marker Efficacy Evaluation

Table 7 shows that both groups exhibited reduced AFP-L3 ratios post-treatment (P<0.01). The observation group also showed significantly decreased DCP levels

(P<0.01), while the control group showed no significant DCP change (P>0.05). No significant differences in AFP levels were observed in either group (P>0.05), suggesting Qizhuhuaji Formula's clinical efficacy in improving AFP-L3 and DCP.

Table 7. Comparison of Tumor Markers Before and After Treatment [M(P25, P75)] | Group | AFP (ng/ml) | AFP-L3 (%) | DCP (mAU/ml) | |——-|————-|————|————| | Observation (pre) | 6.12(2.47,12.58) | 8.05(4.35,12.23) | 19.8(8.57,43.64) | | Observation (post) | 5.5(3.0,10.0) | 6(2.25,8.2)# | 19(7.6,34.5)# | | Control (pre) | 8.25(3.26,12.65) | 8.6(3.52,14) | 25.68(12.4,47.19) | | Control (post) | 8.46(2.9,11.89) | 7.35(4.5,11.175)# | 26(13.5,42.375) |

Note: #P<0.01, P>0.05 vs. pre-treatment; P>0.05 vs. control group post-treatment.

3.2.4 Imaging Efficacy Evaluation Results

Tables 8-10 demonstrate that the observation group showed significant reduction in lesion diameter post-treatment (P<0.01), while the control group showed no significant change (P>0.05). The observation group's total improvement rate was 35.29% with 50% stability rate, compared to the control group's 20% and 43.33%, respectively, showing a therapeutic advantage without statistical significance (P>0.05). Notably, all 3 cured cases in the observation group were RN patients, suggesting favorable effects of Chinese medicine on liver regenerative nodules.

Table 8. Comparison of Lesion Diameter Before and After Treatment (x±s) | Group | Pre-treatment Diameter (mm) | Post-treatment Diameter (mm) | |——-|————————|————————| | Observation | 11.56$±5.97|9.76±6.56# △ ||*Control*|11.47±6.96|11.27±$6.85 |

Note: #P<0.01, P>0.05 vs. pre-treatment; P>0.05 vs. control group post-treatment.

Table 9. Efficacy Comparison of Different Lesion Types | Group | Lesion Type | n | Cured | Remission | Stable | Progression | Improvement Rate | Stability Rate | |——-|————-|—|——-|————|——|————-|————| | Observation | Single | 20 | 3 | 6 | 9 | 2 | 45.00% | 45.00% | | Observation | Multiple | 14 | 0 | 3 | 8 | 3 | 21.43% | 57.14% | | Control | Single | 16 | 0 | 2 | 10 | 4 | 12.50% | 37.50% | | Control | Multiple | 14 | 0 | 4 | 5 | 5 | 28.57% | 35.71% |

Note: All P>0.05 for inter-group comparisons of improvement and stability rates.

Table 10. Total Efficacy Comparison of Lesion Diameter Between Groups | Group | n | Cured | Remission | Stable | Improvement Rate | Stability

Rate | |——-|—|——-|———|——|————–|————-| | Observation | 34 | 3 | 9 | 17 | 35.29% | 50.00% | | Control | 30 | 0 | 6 | 13 | 20.00% | 43.33% |

Note: P>0.05 for both improvement and stability rate comparisons.

3.2.5 Liver Cancer Incidence Comparison

During the treatment period, no liver cancer cases occurred in the observation group versus 1 case in the control group. During the 48-week follow-up, 3 observation group patients (8.82%) and 4 control group patients (16.67%) progressed to HCC. The observation group's lower incidence showed no statistical significance (P>0.05). All 3 HCC cases in the observation group were males over 40 with post-hepatitis B cirrhosis, 2 with family history and long-term alcohol use. Among 5 HCC cases in the control group, 4 were males over 40, 4 had post-hepatitis B cirrhosis, 3 had family history, and 4 had long-term alcohol use—consistent with known HCC risk factors and the high carcinogenic potential of HGDN, suggesting that both HGDN and LGDN patients require active intervention and close monitoring.

3.2.6 Complication Rate Comparison

During follow-up, the observation group had 2 cases of ascites and 1 case of upper gastrointestinal bleeding (8.82% complication rate), while the control group had 5 ascites cases, 2 upper gastrointestinal bleeding cases, and 2 hepatic encephalopathy cases (30% complication rate). The observation group's significantly lower complication rate (P<0.05) demonstrates that Qizhuhuaji Formula combined with conventional therapy offers advantages in reducing cirrhosis complications, improving prognosis, and decreasing mortality.

3.3 Safety Profile

Throughout the observation period, no abnormal safety indicators were detected in either group. The observation group reported 1 case of mild nausea and 1 case of mild abdominal pain/diarrhea, while the control group had 2 cases of mild diarrhea and 1 case of pruritus. All cases were managed symptomatically without discontinuation, with no statistically significant difference between groups (P>0.05).

Discussion

The pathogenesis of HCC precancerous lesions involves progression from dysplastic foci (DF) to dysplastic nodules (DN), with DN further classified as LGDN or HGDN based on cellular atypia. Major etiological factors include cirrhosis, HBV/HCV infection, metabolic-associated fatty liver disease, and long-term

carcinogen exposure. Damaged hepatocytes undergoing restoration and regeneration gradually alter their biological characteristics, while carcinogenic factors activate oncogenes and suppress tumor suppressor genes. Active angiogenesis during chronic inflammation and fibrosis provides conditions for dysplastic proliferation and nodule formation. Pathological diagnosis remains the gold standard, but poor patient compliance with liver biopsy limits clinical application, making imaging and serology the primary diagnostic modalities. Current Western medicine management relies mainly on surveillance, with local ablation or surgical resection recommended for HGDN when necessary. However, standardized treatment protocols are lacking, and questions regarding optimal intervention timing and overtreatment prevention require further investigation.

As a country with high HCC burden, China has increasingly focused on HCC prevention and treatment. Chinese medicine's "preventive treatment" theory, holistic approach, and flexible syndrome-based treatment methods demonstrate emerging advantages, particularly in "preventing disease before onset" and "preventing progression after disease onset." While Western medicine primarily employs surveillance and surgical resection without definitive preventive protocols, Chinese medicine's flexible, holistic approach can fill therapeutic gaps, serving as either primary treatment or adjunctive therapy to reduce side effects and enhance efficacy throughout disease management.

"Preventing disease before onset" refers to active Chinese medicine intervention during chronic liver disease and cirrhosis stages, treating the primary disease while regulating the body's dynamic yin-yang balance to block disease progression. "Preventing progression after onset" means that after precancerous nodules develop, Chinese medicine intervention can effectively alleviate symptoms, improve quality of life, and achieve simultaneous improvement of "disease, syndrome, and symptoms."

Our research team has studied HCC precancerous lesions for years with extensive clinical experience. Qizhuhuaji Formula, developed by our mentor, has produced satisfactory clinical outcomes. The pathogenesis primarily involves "deficiency of vital qi and excess of pathogenic factors"—weak vital qi and declining organ function impair resistance to pathogenic invasion and elimination, allowing pathogen accumulation and eventual formation of blood stasis, phlegm, and toxin that develop into the disease. The liver and spleen are the main affected organs. The liver governs dredging and regulates qi movement; the spleen governs transformation and is the source of qi and blood generation. In Five Element theory, liver (wood) and spleen (earth) are interrelated. Normal liver dredging ensures proper spleen qi ascending/descending and transformation functions, maintaining physiological activities. External damp-heat or pestilent toxins damaging liver function cause liver qi stagnation, which can invade the stomach and disrupt spleen-stomach qi dynamics, impairing transformation and increasing susceptibility to external pathogens. Conversely, excessive liver dredging (overactive wood) can restrain earth and affect spleen function. Therefore, supporting vital qi should focus on soothing the liver and

strengthening the spleen. Pathogenic excess is the direct cause of disease formation, often secondary to viral hepatitis and cirrhosis. External damp-heat-cold pathogens interact with pestilent toxins, obstructing qi movement and damaging the liver-spleen. Insufficient vital qi with exuberant pathogenic qi leads to pathogen retention, which over time generates phlegm, stasis, turbidity, and toxin. Without dispersing pathogenic factors and supporting vital qi, cancerous masses form. Thus, pathogen elimination should focus on activating blood, dispersing accumulation, resolving stasis, and detoxifying. The primary pathomechanisms in our study population were "stasis," "toxin," and "deficiency," requiring simultaneous vital qi support and pathogen elimination. Qizhuhuaji Formula achieves this through soothing the liver, strengthening the spleen, and resolving stasis to detoxify, yielding satisfactory results.

Our mentor emphasizes that the disease location is in the liver, following the principle "When seeing liver disease, knowing it transmits to the spleen, first strengthen the spleen." Robust spleen qi ensures normal liver dredging function and nourishes liver substance. Additionally, since this disease often has a chronic liver disease background with prolonged illness affecting the kidney, liver-kidney deficiency represents an objective internal factor. Therefore, HCC precancerous lesions should be treated by syndrome differentiation of the liver, spleen, and kidney triad. While supporting vital qi and dispelling pathogenic factors, special attention must be paid to protecting the spleen-stomach, emphasizing soothing the liver, strengthening the spleen, and activating blood methods. Medication focuses on three aspects: benefiting spleen-nourishing liver, moving qi-activating blood, and detoxifying-dispersing nodules. Clinical treatment integrates modern pharmacological research, routinely incorporating herbs with anti-cancer effects such as *Hedyotis diffusa*, *Paris polyphylla*, and *Scutellaria barbata*.

The specific Qizhuhuaji Formula composition: *Astragalus* 60g and *Atractylodes* 20g strengthen the spleen and boost qi to treat deficiency. According to *Medical Records Synthesizing Chinese and Western Medicine*, astragalus is warm and ascending, similar to liver wood nature, excelling at liver supplementation. *Cyperus* soothes the liver and regulates qi to harmonize qi movement, which Huang Gongxiu described as "entering liver-gallbladder channels, relieving stagnation and dispersing nodules, particularly effective for resolving melancholy." These two herbs serve as the sovereign drugs. *Atractylodes* supplements spleen qi; *Poria* and *Coix* strengthen the spleen and transform dampness; *Dioscorea* strengthens the spleen and nourishes yin; *Curcuma* moves qi and relieves stagnation. These assist the sovereign drugs in achieving the effects of soothing the liver, strengthening the spleen, and boosting qi, serving as minister drugs. *Trionyx* softens hardness, disperses nodules, and nourishes liver-kidney yin. Combined with astragalus, it supplements qi without dryness and promotes diuresis without injuring yin. *Gallus gallus* eliminates accumulation and stagnation, combined with *Trionyx* to transform stasis and disperse masses—Zhang Xichun praised it as "capable of eliminating accumulations anywhere in the viscera." *Fritillaria* and *Ostrea* also soften hardness and disperse nodules. *Angelica* activates blood while nourishing blood; Huang Yuanyu considered it able to "nour-

ish blood and enrich the liver, moisten wood and clear wind, activating minute collaterals." Combined with astragalus, it boosts qi and generates blood. *Curcuma zedoaria*, *Scorpio*, and *Scolopendra* all activate blood, dispel stasis, and unblock collaterals. *Hedyotis diffusa*, *Paris polyphylla*, and *Verbena* together clear heat, detoxify, and disinhibit dampness while reducing swelling. These serve as assistant drugs. Additionally, *Dioscorea* combined with *Gallus gallus* strengthens the spleen, eliminates food stagnation, and protects stomach qi to prevent damage from detoxifying and nodule-dispersing herbs. *Glycyrrhiza* not only supplements spleen qi and relieves urgency and pain but also harmonizes all medicinals as the envoy drug. The entire formula achieves the effects of strengthening the spleen, soothing the liver, transforming stasis, and dispersing accumulation, with additional functions of transforming dampness and detoxifying.

This study demonstrates that Qizhuhuaji Formula combined with conventional Western medicine effectively improves clinical syndromes and liver function in HCC precancerous lesion patients while reducing liver cancer incidence and complication rates. The results confirm that liver depression and spleen deficiency with phlegm-blood stasis represents the key pathomechanism, and the therapeutic method of soothing the liver, strengthening the spleen, and resolving stasis to detoxify is effective and worthy of clinical promotion. However, limitations include small sample size and short follow-up duration due to study period and funding constraints, potentially introducing bias. Future multi-center, large-sample prospective and retrospective studies with extended follow-up are needed to obtain more accurate and objective data. While current research suggests positive prognostic effects of Chinese medicine, systematic theoretical explanations and standardized treatment protocols are lacking. Whether Chinese medicine can inhibit the formation of dysplastic nodules and how to determine optimal intervention timing remain unclear, hindering clinical promotion. Deeper, more rigorous research is required to provide systematic, scientific theoretical explanations and establish Chinese medicine diagnostic and therapeutic standards to better guide and promote Chinese medicine development.

References

[1] National Health Commission of the People's Republic of China. Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2022 Edition). *Cancer Research on Prevention and Treatment*, 2022; 49(3): 251-276.
[2] Rui R, Dong X, Meng BB, et al. Research progress on active components of Chinese medicine intervening in signaling pathways related to liver cancer precancerous lesion development. *Liaoning Journal of Traditional Chinese Medicine*, 2019; 46(05): 1114-1116.
[3] Renzulli M, Biselli M, Brocchi S, et al. New hallmark of hepatocellular carcinoma, early hepatocellular carcinoma and high-grade dysplastic nodules on Gd-EOB-DTPA MRI in patients with cirrhosis: A new diagnostic algorithm. *Gut*, 2018; 67(9): 1674-1682.

[4] Editorial Board of *Chinese Journal of Hepatology*, et al. Multidisciplinary Expert Consensus on the Diagnosis and Treatment of Hepatocellular Carcinoma Precancerous Lesions (2020 Edition). *Journal of Clinical Hepatology*, 2020; 36(3): 516-517.
[5] Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis*, 2010; 30(1): 52-60.
[6] Professional Committee for Prevention and Control of Hepatobiliary and Pancreatic Diseases, Chinese Preventive Medicine Association. Guidelines for Stratified Screening and Surveillance of Primary Liver Cancer (2020 Edition). *Journal of Clinical Hepatology*, 2021; 37(2): 286-295.
[7] Ge JB, Xu YJ, Wang C. *Internal Medicine*. Beijing: People's Medical Publishing House, 2018, 9: 415-418.
[8] Zhou KQ, Zhou C, Wang Z. Research progress on hepatic dysplastic nodules. *Journal of Surgery: Theory and Practice*, 2018; 23(03): 286-
[9] Sciarra A, di Tommaso L, Nakano M, et al. Morphophenotypic changes in human multistep hepatocarcinogenesis with translational implications. *J Hepatol*, 2016; 64(1): 87-93.
[10] Renzulli M, Biselli M, Brocchi S, et al. New hallmark of hepatocellular carcinoma, early hepatocellular carcinoma and high-grade dysplastic nodules on Gd-EOB-DTPA MRI in patients with cirrhosis: A new diagnostic algorithm. *Gut*, 2018; 67(9): 1674-1682.
[11] Kudo M, Matsui O, Izumi N, et al. JSH consensus-based clinical practice guidelines for the management of hepatocellular carcinoma: 2014 update by the Liver Cancer Study Group of Japan. *Liver Cancer*, 2014; 3(3-4): 458-568.
[12] Huang JJ, Pan Z, Huang HN, et al. Research progress of Chinese medicine on liver cancer precancerous lesions. *Guiding Journal of Traditional Chinese Medicine and Pharmacy*, 2014; 20(3): 136-137.
[13] Zhang XC, Wei HL, Li JT, et al. Analysis of the effect of external application and enema nursing measures combined with Yipi Yanggan Formula on patients with liver cancer precancerous lesions. *Sichuan Traditional Chinese Medicine*, 2017; 35(7): 212-215.
[14] Chen XT, He C, Li JT, et al. Current status of Chinese medicine in preventing and treating liver cancer precancerous lesions. *Chinese Journal of Integrated Traditional and Western Medicine on Liver Diseases*, 2016; 26(5): 314-316.

Note: Figure translations are in progress. See original paper for figures.