

Clinical Study on Qiling Ruangan Prescription Combined with Antiviral Therapy for Chronic Hepatitis B Liver Fibrosis

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Abstract: To investigate the clinical efficacy of Qiling Ruangan Prescription combined with antiviral therapy in the management of chronic hepatitis B-related liver fibrosis, this study retrospectively analyzed the medical records of 124 patients admitted to our hospital between December 2020 and December 2022, who were stratified into two groups based on whether they received Qiling Ruangan Prescription treatment. Liver function parameters, four liver fibrosis markers, Aspartate Aminotransferase-to-Platelet Ratio Index (APRI), Liver Stiffness Measurement (LSM), and traditional Chinese medicine (TCM) syndrome scores were compared between the two groups before and after treatment. The results demonstrated that after treatment, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBIL), hyaluronic acid (HA), laminin (LN), and chitinase-3-like protein 1 (CHI3L1) were significantly reduced in both groups ($P < 0.05$), with a more remarkable decrease observed in the treatment group ($P < 0.05$). No statistically significant differences in procollagen III N-terminal peptide (PIIINP) and type IV collagen (CIV) were detected between the two groups either pre- and post-treatment or inter-group ($P > 0.05$). Meanwhile, APRI, LSM, and TCM syndrome scores were significantly improved in both groups ($P < 0.05$), and the therapeutic effect in the treatment group was superior to that in the control group ($P < 0.05$). In conclusion, compared with antiviral monotherapy, Qiling Ruangan Prescription combined with antiviral therapy can more effectively improve liver function, optimize liver fibrosis markers, and alleviate TCM syndrome scores in patients with chronic hepatitis B-related liver fibrosis, exerting a more prominent anti-fibrotic effect.

1. Introduction

Hepatic fibrosis (HF) refers to an aberrant wound-healing response triggered by chronic liver

injury from various etiologies, including chronic hepatitis B (CHB), chronic hepatitis C, and alcoholic fatty liver disease. Pathologically, it is characterized by the diffuse and excessive deposition of extracellular matrix (ECM) in the liver [1]. With persistent injury, pro-inflammatory mechanisms are activated, leading to disruption of the normal hepatic architecture and function. Over time, scar tissue progressively replaces functional liver parenchyma, potentially progressing to liver cirrhosis, hepatocellular carcinoma (HCC), and even death [2]. As such, hepatic fibrosis represents a critical determinant of mortality in patients with chronic liver diseases. Globally, the prevalence of hepatic fibrosis among individuals with chronic liver disease is estimated at 1%–2%, with over one million annual deaths attributable to liver cancer or liver failure resulting from fibrosis progression [3, 4]. China bears a high burden of hepatitis B, and hepatitis B virus (HBV) infection remains a leading cause of hepatic fibrosis. Persistent HBV infection, if not effectively cleared, almost invariably induces fibrotic changes in the liver. Importantly, histological studies have demonstrated that hepatic fibrosis is reversible at certain stages [5], and timely intervention can slow or even reverse its progression. Therefore, developing rational and effective treatment strategies for hepatic fibrosis continues to be a major focus of hepatology research. Current Western medical approaches to HBV-related hepatic fibrosis primarily target etiological control (e.g., antiviral therapy) and hepatoprotective/anti-inflammatory strategies, yet there remains a lack of direct and effective anti-fibrotic agents [6]. Traditional Chinese medicine (TCM) offers unique advantages in this context. Drawing on decades of clinical experience and theoretical inheritance, contemporary TCM practitioners contend that the pathogenesis of HBV-related hepatic fibrosis involves "phlegm," "turbidity," "stasis," and "deficiency," with healthy qi (zhengqi) deficiency and blood stasis constituting the core pathological basis [7]. In light of this, the present study aimed to evaluate the clinical efficacy of Qiling Ruangan Decoction (QRD) combined with antiviral therapy in patients with chronic hepatitis B-associated hepatic fibrosis, with the goal of providing new insights and a reference for integrated Chinese-Western medicine treatment of this condition.

2. Materials and Methods

2.1 Clinical Data and Grouping

A total of 124 patients were enrolled in this study, all of whom had chronic hepatitis B-related hepatic fibrosis and sought care at Xixi Hospital of Hangzhou between December 2020 and December 2022. Among these, 55 patients received the traditional Chinese and Western medicine (TCWM) combination therapy, while 69 patients received Western medicine therapy alone. The manuscript subsequently presents the diagnostic criteria, as well as the inclusion and exclusion criteria adopted for TCWM in conjunction with Western medicine, to delineate eligibility and ensure comparability between groups.

2.2 Diagnostic Criteria, Inclusion and Exclusion Criteria for Traditional Chinese Medicine and Western Medicine

2.2.1 Western Medicine Diagnostic Criteria

Diagnostic criteria were referenced from the Guidelines for the Prevention and Treatment of Chronic Hepatitis B (2019 Edition) [8] and the Guidelines for the Integrated Traditional Chinese and Western Medicine Diagnosis and Treatment of Liver Fibrosis [9], as follows: 1) History of hepatitis B or positive hepatitis B surface antigen (HBsAg) for more than 6 months; 2) Abnormal elevation of serum hyaluronic acid (HA), laminin (LN), type IV collagen (CIV), procollagen III N-terminal peptide (PIIINP), and aspartate aminotransferase-to-platelet ratio index (APRI); 3) Liver B-

ultrasound findings including uneven liver capsule surface, enhanced intrahepatic echo, uneven echo distribution, unclear vascular direction, and widened portal vein diameter; 4) Liver stiffness measurements (LSM) were interpreted according to the criteria in the Expert Consensus on the Clinical Application of Transient Elastography (TE) [10]: 1) For CHB patients with normal bilirubin and ALT < 5 × upper limit of normal (ULN): LSM < 7.4 kPa excludes advanced liver fibrosis; LSM ≥ 9.4 kPa suggests significant liver fibrosis; LSM < 10.6 kPa excludes cirrhosis; LSM ≥ 12.4 kPa (10.6 kPa when ALT < 2 × ULN) suggests advanced liver fibrosis; LSM ≥ 17.0 kPa suggests cirrhosis; 2) For CHB patients with normal bilirubin and elevated ALT: LSM < 6.0 kPa excludes advanced liver fibrosis; LSM < 9.0 kPa excludes cirrhosis; LSM ≥ 9.0 kPa suggests advanced liver fibrosis; LSM ≥ 12.0 kPa suggests cirrhosis.

2.2.2 Traditional Chinese Medicine (TCM) Diagnostic Criteria

Diagnostic criteria were formulated with reference to the Guidelines for the Integrated Traditional Chinese and Western Medicine Diagnosis and Treatment of Liver Fibrosis (2019 Edition) [9], the Guiding Principles for Clinical Research of New Chinese Medicines (Trial) [11], and Professor Bao Jianfeng's long-term clinical experience in differentiating and treating chronic hepatitis B-associated liver fibrosis. Through comprehensive analysis of the disease, the syndrome type was summarized as "spleen deficiency with dampness obstruction and phlegm-stasis intermingling", with the following TCM diagnostic criteria:

Main symptoms: 1) Discomfort or fixed, non-migratory hypochondriac pain; 2) Fatigue and weakness; 3) Limb heaviness and discomfort;

Secondary symptoms: 1) Poor appetite and postprandial abdominal distension; 2) Nausea and vomiting; 3) Dry mouth and bitter taste; 4) Sallow complexion; 5) Spider nevi and abdominal wall varicose veins; 6) Sublingual varicosities; 7) Loose or sticky stools; 8) Tongue and pulse manifestations: Swollen tongue, purplish-dark tongue or tongue with petechiae/ecchymoses, thick greasy white tongue coating, and astringent or stringy-astringent pulse;

Diagnosis required the presence of ≥2 main symptoms plus ≥2 secondary symptoms.

2.2.3 Inclusion Criteria

(1) Meeting the above-mentioned TCM and Western medicine diagnostic criteria for chronic hepatitis B-associated liver fibrosis [7-8]; (2) Agreeing to long-term follow-up with relatively complete clinical diagnosis, treatment, and follow-up data; (3) Providing written informed consent.

2.2.4 Exclusion Criteria

(1) Incomplete medical records; (2) Previous or concurrent use of Chinese patent medicines for anti-liver fibrosis; (3) Co-infection with other hepatitis viruses; (4) Pregnant women; (5) Patients with mental illnesses; (6) Patients with tumors.

2.3 Treatment Regimens

(1) Qiling Ruangan Decoction (QRD) composition: Coix seed (30 g), Astragalus membranaceus (15 g), Poria cocos (15 g), Rhizoma zedoariae (10 g), Bupleurum chinense (9 g), Amomum villosum (6 g), Polygonum orientale (6 g), Pheretima aspergillum (6 g), Campsis grandiflora (9 g);

(2) Antiviral treatment: Entecavir, Tenofovir Disoproxil Fumarate, Tenofovir Alafenamide Fumarate, Lamivudine, or Telbivudine (LdT).

2.4 Grouping and Intervention

Treatment group: Qiling Ruangan Decoction combined with antiviral therapy. QRD was administered on the basis of antiviral treatment, with continuous treatment for ≥ 3 months;

Control group: Antiviral therapy alone. Patients received antiviral treatment only, with continuous treatment for ≥ 6 months.

2.5 Outcome Measures

Efficacy evaluation indicators included: 1) Liver fibrosis biomarkers: HA, LN, CIV, PIIINP, and chitinase-3-like protein 1 (CHI3L1); 2) Liver function parameters: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (TBIL); 3) APRI: Calculated using the formula: $APRI = [(AST/ULN) / PLT (10^9/L)] \times 100$; 4) Imaging assessment (LSM): Liver stiffness was measured using a transient elastography scanner (FibroTouch, Wuxi Haiskel Co., Ltd.) before and after treatment [9]; 5) TCM clinical syndrome efficacy: Evaluated using a TCM syndrome scoring scale before and after treatment.

2.6 Statistical Methods

Data were analyzed using SPSS 27.0 statistical software. Propensity score matching (PSM) was performed via logistic regression to balance baseline characteristics between the two groups. Measurement data conforming to normal distribution were expressed as mean $\pm$ standard deviation and compared using the t-test. Measurement data not conforming to normal distribution were expressed as median and interquartile range and analyzed using non-parametric tests. Categorical data were expressed as frequencies and percentages and compared using the χ^2 test. A two-tailed $P < 0.05$ was considered statistically significant.

3. Results

3.1 Comparison of Liver Function Indicators before and After Treatment

There was no statistically significant difference in liver function between the two groups before treatment ($P > 0.05$). Compared with pre-treatment levels, both groups showed statistically significant decreases in AST, ALT, ALP, and TBIL post-treatment ($P < 0.05$). Compared with the control group, the treatment group exhibited significantly greater reductions in ALT, AST, ALP, and TBIL levels ($P < 0.05$). See Table 1.

Table 1 Comparison of serum ALT, AST, ALP, and TBIL levels before and after treatment in both groups

Variable	Group	Before Treatment	After Treatment	
ALT (U/L)	Treatment Group	58.67 (40.00, 79.55)	25.79 (18.75, 38.00)*#	
	Control Group	60.37 (39.50, 81.50)	29.01 (20.45, 39.25)	
AST (U/L)	Treatment Group	41.25 (25.00, 69.25)	21.54 (15.75, 32.25)*#	
	Control Group	41.72 (24.50, 75.25)	24.20 (18.00, 35.63) *	
ALP (U/L)	Treatment group	113.35 (75.75, 146.50)	53.25 (39.75, 63.25)*#	
	Control Group	126.04 (88.00, 162.25)	60.33 (50.75, 64.00)*	
TBIL ($\mu\text{mol/L}$)	Treatment Group	22.35 (11.46, 21.34)	14.16 (11.49, 16.53) *#	
	Control Group	23.16 (18.15, 28.94)	16.75 (11.46, 21.34) *	

Note: *Compared with pre-treatment in this group, $P < 0.05$; #Compared with post-

treatment in the control group, $P < 0.05$.

3.2 Comparison of Four Liver Fibrosis Markers and CHI3L1 Levels Before and After Treatment

There was no statistically significant difference in the four liver fibrosis markers and CHI3L1 levels between the two groups before treatment ($P > 0.05$). Compared with pre-treatment levels, both groups showed a significant decrease in HA, LN, and CHI3L1 levels after treatment, with statistical significance ($P < 0.05$). Compared with the control group, the treatment group demonstrated superior improvement in HA, LN, and CHI3L1 levels ($P < 0.05$). Pre- and post-treatment comparisons within both groups, as well as intergroup comparisons, showed no statistically significant differences in PIIINP and CIV levels ($P > 0.05$), as shown in Table 2.

Table 2 Comparison of four liver fibrosis markers and CHI3L1 levels before and after treatment between the two groups

Variable	Group	Before Treatment	After Treatment
HA (ng/ml)	Treatment Group	116.13 (73.37, 144.55)	68.54 (48.40, 82.00)* #
	Control group	115.25 (78.37, 158.89)	79.58 (56.57, 96.07)*
PIIINP (ng/mL)	Treatment Group	22.60 (13.93, 28.60)	19.46 (15.52, 22.58) $\triangle\circ$
	Control Group	21.68 (16.00, 27.00)	19.69 (15.57, 21.16) $\triangle\circ$
CIV (ng/mL)	Treatment Group	20.00 (14.77, 25.65)	19.90 (14.67, 20.52) $\triangle\circ$
	Control Group	21.27 (15.85, 26.95)	18.57 (16.50, 20.75) $\triangle\circ$
LN (ng/ml)	Treatment group	37.08 (26.20, 44.80)	30.28 (26.72, 33.10)* #
	Control group	34.15 (25.70, 47.95)	30.05 (25.55, 33.50)*
CHI3L1 (ng/mL)	Treatment group	70.99 (39.83, 96.66)	41.64 (25.07, 52.38)* #
	Control Group	74.222 (41.91, 98.43)	48.57 (26.82, 55.48)*

Note: $\triangle$ Compared with pre-treatment in this group, $P > 0.05$; *Compared with pre-treatment in this group, $P < 0.05$; #Compared with post-treatment in the control group, $P < 0.05$; $\circ$ Compared with post-treatment in the control group, $P > 0.05$.

3.3 Comparison of APRI Scores before and After Treatment

Pre-treatment APRI scores showed no statistically significant difference between groups ($P > 0.05$). Compared with pre-treatment levels, post-treatment APRI scores differed significantly between groups ($P < 0.05$). The treatment group showed statistically significant improvement compared with the control group ($P < 0.05$), as shown in Table 3.

Table 3 Comparison of APRI Scores before and After Treatment in the Two Groups of Patients

Variable	Group	Before Treatment	After Treatment	<i>P Value</i>
APRI	Treatment Group	0.71 (0.45, 0.87)	0.35 (0.23, 0.42)*#	0.001
	Control Group	0.67 (0.42, 0.86)	0.42 (0.27, 0.42)*	0.001

Note: *Compared with pre-treatment values in this group, $P < 0.05$; #Compared with post-treatment values in the control group, $P < 0.05$.

3.4 Changes in LSM before and After Treatment in Both Groups

Table 4 Comparison of LSM Values before and After Treatment in Both Groups

Variable	Group	Before Treatment	After Treatment	<i>P Value</i>
LSM	Treatment Group	10.68 (8.54, 12.05)	7.96 (6.17, 9.52)* #	0.001
	Control Group	10.49 (8.60, 11.92)	8.61 (6.60, 10.27)*	0.001

Note: *Compared with pre-treatment in this group, $P < 0.05$; #Compared with post-treatment in the control group, $P < 0.05$.

There was no statistically significant difference in LSM between the two groups prior to treatment ($P > 0.05$). Compared with pre-treatment levels, LSM decreased significantly in both groups post-treatment ($P < 0.05$). The treatment group exhibited a greater reduction than the control group, with a statistically significant difference ($P < 0.05$), as shown in Table 4.

3.5 Changes in Traditional Chinese Medicine Syndrome Scores before and After Treatment

Pre-treatment TCM syndrome scores showed no significant difference between groups ($P > 0.05$). Post-treatment scores decreased in both groups ($P < 0.05$), with the treatment group exhibiting significantly lower scores than the control group ($P < 0.05$), as shown in Table 5.

Table 5 Comparison of Traditional Chinese Medicine Syndrome Scores before and After Treatment in Patients with

Variable	Group	Before Treatment	After Treatment
TCM Syndrome Score	Treatment Group	13.51 ± 8.40	8.29 ± 5.88* #
	Control group	13.83 ± 9.15	9.63 ± 6.88*

Note: *Compared with pre-treatment values in this group, $P < 0.05$; #Compared with post-treatment values in the control group, $P < 0.05$.

4. Discussion

Liver fibrosis refers to the formation of fibrous scars in the liver following human infection with the hepatitis B virus (HBV). It represents an inevitable pathological progression in all chronic liver diseases. While antiviral therapy can ameliorate liver fibrosis in some patients with chronic hepatitis B (CHB), it fails to fully halt fibrosis progression [10, 11]. A considerable proportion of patients with liver fibrosis exhibit suboptimal responses to antiviral therapy, with persistent disease that may ultimately progress to liver cirrhosis or hepatocellular carcinoma [12, 13].

Traditional Chinese Medicine (TCM) lacks a specific diagnostic denomination for liver fibrosis. However, based on its clinical manifestations—including hypochondriac distension and pain, jaundice, and subcostal masses—it can be categorized under TCM disease entities such as "huangdan (jaundice)", "xietong (hypochondrial pain)", and "jiju (mass accumulation)". Hepatitis B-associated liver fibrosis primarily arises when patients are afflicted by damp-heat toxins that accumulate in the zhongjiao (middle jiao), impairing the transportation and transformation functions of the spleen and stomach. Prolonged illness depletes zhengqi (vital energy), resulting in insufficient qi to expel pathogens. This subsequently leads to zang-fu organ dysfunction, qi-blood-yin-yang imbalance, liver-spleen disharmony, and impaired spleen transformation, ultimately causing blood stasis obstruction and deficient liver qi dispersion, which triggers the condition [14, 15].

Based on this pathogenesis, Professor Bao Jianfeng formulated Qiling Ruangan Decoction (QRD, Astragalus-Poria Liver-Softening Decoction). Following the TCM sovereign-minister-assistant-

envoy herb principle: *Astragalus membranaceus* (Huangqi) serves as the sovereign herb to replenish qi, strengthen the spleen, and expel pathogens; *Poria cocos* (Fuling) and *Coix lacryma-jobi* seeds (Yiyiren) act as co-sovereign herbs to fortify the spleen, drain dampness, and support spleen-stomach transformation to ensure a steady source of nutritive blood. As minister herbs, *Polygonum orientale* L. (safflower seeds) eliminate stasis, disperse accumulations, and drain dampness; *Pheretima aspergillum* (earthworm) excels at unblocking collaterals due to its penetrating property; *Campsis grandiflora* (*Campsis radicans*) promotes blood circulation to resolve stasis; and *Rhizoma zedoariae* (*Curcuma zedoaria*) regulates qi to break blood stasis. *Bupleurum chinense* DC. (*Bupleurum*) functions as the assistant herb to soothe the liver, guide the formula to the liver meridian, and relieve liver qi stagnation. *Fructus amomi* (*Amomum villosum*) acts as a key herb to awaken the spleen and regulate the stomach, subtly conforming to the TCM principle of addressing liver excess and spleen deficiency.

Overall, the formula adheres to the fundamental therapeutic principles of promoting blood circulation to resolve stasis, fortifying the spleen, and draining dampness. It embodies TCM's understanding of disease and therapeutic approach that recognizes concurrent liver-spleen disorders, addresses both qi and blood, and integrates pathogenic elimination with tonification.

5. Conclusion

The results of this study demonstrated that compared with baseline, post-treatment levels of ALT, AST, ALP, TBIL, HA, LN, and CHI3L1 were significantly reduced in both groups, with a more pronounced decrease observed in the treatment group. This indicates that both therapeutic regimens ameliorated patients' liver fibrosis status, and the treatment group exhibited superior anti-fibrotic efficacy. Furthermore, analyses of liver stiffness measurements (LSM) and APRI scores revealed notable reductions in both groups following treatment, confirming the favorable clinical outcomes of Qiling Ruangan Decoction (QRD, *Astragalus*-*Poria* Liver-Softening Formula) combined with antiviral therapy in patients with hepatitis B virus (HBV)-associated liver fibrosis. Integrating evaluations of liver function indices, clinical symptoms, LSM, four-marker fibrosis panel, and Traditional Chinese Medicine (TCM) syndrome scores, this combined treatment regimen exerts potent anti-fibrotic effects against HBV-associated liver fibrosis, warranting clinical application and broader promotion.

This study has certain limitations. First, it is a single-center retrospective study with a relatively small sample size and a lack of pathological data, which may introduce selection bias. Second, the compliance of patients with actual medication during the follow-up period was not evaluated, potentially leading to bias related to medication adherence. In the future, large-sample, multi-center, prospective studies are warranted to further validate the efficacy of Qiling Ruangan Decoction (QRD) in chronic hepatitis B-associated liver fibrosis. Additionally, basic experimental research is required to confirm its therapeutic effects and explore the underlying mechanisms of action.

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