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Original Article

Entecavir plus Fuzheng Huayu Compound Reduces the Risk of Portal Hypertension-related Complications in Patients with Compensated Hepatitis B Virus-related Cirrhosis: A Post Hoc Analysis Based on Two Randomized Controlled Trials

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Abstract

Background and objectives: Fuzheng Huayu, a patent herbal product, has shown promise in liver fibrosis and cirrhosis. The effect of Fuzheng Huayu on portal hypertension due to cirrhosis and the consequent complications needs further investigation. In this study, we aimed to evaluate the association of adjunctive Fuzheng Huayu plus entecavir with liver-related events and variceal regression in patients with compensated HBV-related cirrhosis.

Methods: A post hoc analysis was conducted using data from two randomized controlled trials implemented at eight clinical centers in China (ClinicalTrials.gov numbers: NCT02945982; NCT02945956). Patients with compensated hepatitis B virus-related cirrhosis were enrolled from October 2017 to March 2021. The primary endpoint was a composite of liver events and the individual components, including variceal bleeding, ascites, overt hepatic encephalopathy, and hepatocellular carcinoma.

Results: A total of 218 participants (Fuzheng Huayu group: 110 and control group: 108; mean age, 51.5 years; 66.5% male; median observational follow-up time, 23.1 months) were included in the primary analysis. The occurrence of total liver events was less frequent in the Fuzheng Huayu group than in the control group (hazard ratio = 0.408 [0.187–0.892], $P = 0.020$). Among the individual components of liver events, the incidence of ascites was significantly lower in the Fuzheng Huayu group than in the control group (1.8% vs. 9.3%, $P = 0.016$). In addition, the rate of variceal regression was significantly higher in the Fuzheng Huayu group (27.3% vs. 10.2%, $P < 0.001$). Finally, there were no significant differences in the occurrence of adverse events between the two groups.

Conclusions: In this post hoc analysis of two randomized controlled trials, adjunctive Fuzheng Huayu plus entecavir was associated with fewer liver-related events, particularly ascites, and a higher rate of variceal regression than entecavir alone in patients with compensated hepatitis B virus-related cirrhosis. These findings warrant confirmation in adequately powered prospective studies.

Keywords: Fuzheng Huayu; Entecavir; Portal hypertension; Cirrhosis; Decompensation; Ascites; Esophageal and gastric varices.
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Introduction

Cirrhosis is an important cause of mortality among patients with chronic liver disease, accounting for 1 million deaths every year globally.[1,2] Hepatitis B virus (HBV) infection is the major cause of cirrhosis worldwide.[3] Portal hypertension, the major complication of cirrhosis, is the pivotal mechanism driving the transition from compensated to decompensated cirrhosis, defined by the presence of ascites, variceal bleeding, hepatic encephalopathy, or hepatorenal syndrome.[4,5] Effective reduction in portal pressure significantly decreases the incidence of complications in patients with cirrhosis and improves survival. Therefore, effective management strategies to reduce the risk of portal hypertension in patients with cirrhosis are urgently needed.

Treatments such as transjugular intrahepatic portosystemic shunt markedly decrease portal pressure but are associated with potential trauma and an increased risk of hepatic encephalopathy.[6,7] Endoscopic interventions, such as ligation and sclerosant or tissue glue injections, mainly target gastroesophageal varices but cannot reduce portal pressure. Nonselective beta-blockers (NSBBs) can efficiently reduce portal pressure and prevent decompensation of cirrhosis while causing hemodynamic adverse effects such as bradycardia and hypotension.[8] Therefore, the search for more powerful and safer alternatives continues. Antifibrotic therapy could reduce intrahepatic resistance and is expected to be a promising treatment for cirrhotic portal hypertension.[9]

Fuzheng Huayu formula (FZHY) is composed of *Salvia miltiorrhiza* Bunge (Danshen; root and rhizome, 8 g), Cordyceps fermentation mycelium powder (Chongcao, 4 g), *Prunus persica* (L.) Batsch (Taoren; seed, 2 g), *Gynostemma pentaphyllum* (Thunb.) Makino (Jiaogulan; whole herb, 6 g), *Schisandra chinensis* (Turcz.) Baill. (Wuweizi; ripe fruit, 2 g), and *Pinus massoniana* Lamb. (Songhuafen; pollen, 2 g).[10] FZHY was approved by the China Food and Drug Administration (No. Z20050546) in 2002 to treat liver fibrosis in China,[11,12] serving as an exemplary representative of a therapy with the ability to effectively delay and regress liver fibrosis.[13,14] Furthermore, a phase 2b, randomized, placebo-controlled, double-blind, multicenter study (NCT00854087) enrolling 118 patients with active hepatitis C virus infection who had failed prior anti-hepatitis C virus therapy or had an intolerance to or refused interferon-based therapy from eight liver centers in the U.S. showed that FZHY produced antifibrotic effects in patients with baseline Ishak F3 and F4 fibrosis stages.[15] Given that FZHY can degrade the extracellular matrix deposited in the liver and improve hepatic sinusoidal capillarization, the agent may reduce intrahepatic vascular resistance, thereby contributing to an improvement in portal hypertension.[16] We hypothesized that FZHY may prevent the progression of portal hypertension by targeting the underlying hepatic fibrotic process.

Notably, clinically significant portal hypertension (CSPH), defined as a hepatic venous pressure gradient ≥ 10 mm Hg, is associated with the development of both esophageal varices and decompensation events.[8] There have been reports that removal or suppression of the primary etiological factor may lead to meaningful decreases in CSPH in most patients and substantially reduce the risk of hepatic decompensation.[5] Previous observations have indicated that FZHY may have effects against portal hypertension but those studies were often limited by small sample sizes,[17] retrospective designs, or surrogate endpoints. Our current study is the first multicenter post hoc analysis of two randomized controlled trials (RCTs) specifically designed to evaluate the efficacy of FZHY on clinical outcomes of portal hypertension, namely, portal hypertension-related complications and decompensation events, in patients with compensated HBV-related cirrhosis.

Materials and methods

Study design

This study is a post hoc analysis of two open-label, multicenter RCTs, with randomization preserved (Trial registration: NCT02945982; NCT02945956). The ethical approval was obtained from the Ethics Committee of Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine (approval No. 2017-560-43). From October 2017 to March 2021, the study was performed in accordance with the ethical standards of the Declaration of Helsinki (as revised in 2024), and written informed consent was obtained from each participant. The patients with compensated HBV-related cirrhosis and no or small esophageal varices, or patients with compensated HBV-related cirrhosis and medium or large esophageal varices, were enrolled in two RCTs, respectively, to evaluate the efficacy of FZHY in preventing portal hypertension in these two subpopulations. Patients were randomized 1:1 to receive either entecavir or FZHY plus entecavir, in addition to guideline-directed therapy for cirrhosis. Additionally, participants with high-risk esophageal varices identified by gastroscopy screening received carvedilol treatment.[18] In this study, carvedilol was administered to participants with medium/large varices, whereas those with no or small varices did not receive the drug. The sample size calculation procedures for the two RCTs were described in our study design protocol, which was published in the *Journal of Clinical Trials* in 2025.[18]

Study population

Eligible participants were (1) aged between 18 and 65 years; (2) had a history of hepatitis B or were HBsAg-positive for more than 6 months; (3) had been diagnosed with cirrhosis based on clinical presentation, laboratory tests, imaging studies, or liver biopsy; (4) had HBV DNA < 50 IU/mL during entecavir therapy; (5) had a

Child-Pugh score < 9; and (6) had the capacity to provide informed consent. Those who met any of the following criteria were excluded: (1) taking antifibrotic drugs within the past 6 months; (2) chronic liver disease of any other etiology; (3) concomitant liver cancer; (4) Child-Pugh score ≥9, and decompensated cirrhosis; (5) a history of mental illness or uncontrolled epilepsy; (6) uncontrolled diabetes; (7) a history of hemolytic anemia caused by hemoglobinopathy or other causes, such as autoimmune hemolytic anemia; (8) severe underlying diseases, including chronic respiratory failure, renal failure, or circulatory failure; (9) undergoing orthotopic organ transplantation (such as liver, heart, lung, or kidney transplantation) or bone marrow/stem cell transplantation; (10) immunodeficiency, such as human immunodeficiency virus infection; (11) pregnancy or lactation; (12) allergy to FZHY or entecavir; or (13) participation in other clinical trials.

Procedures and follow-up

Patients in the FZHY group were treated with an oral dose of FZHY (4 tablets, 1.6 g per dose) after randomization, 3 times a day for 96 weeks. Treating physicians were instructed to provide anti-HBV entecavir therapy, cirrhosis guideline-directed treatments, and supportive treatments unless contraindicated or declined by the patients, their family members, or hepatologists. At baseline, clinical history, physical examination, blood tests, upper gastrointestinal endoscopy, and abdominal ultrasonography were performed. Clinical evaluations included history and physical examination (blood pressure, heart rate, height, weight, shifting dullness, hepatomegaly, and splenomegaly). Laboratory tests included red blood cell count, hemoglobin, white blood cell count, platelet count, C-reactive protein, total bilirubin, direct and indirect bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, blood urea nitrogen, serum creatinine, potassium, sodium, α-fetoprotein, prothrombin time, blood ammonia, fecal occult blood test, and HBV DNA. Endoscopic evaluations included the size and location of varices.

Outcomes were assessed at 3-month intervals during the 96-week efficacy follow-up period, followed by an additional observational follow-up of approximately 12 months for clinical events, with a maximum follow-up of approximately 36 months. At each follow-up visit, red blood cell count, fecal occult blood test, blood ammonia, abdominal ultrasound, and/or endoscopic evaluations were performed. Patients discontinued the trial treatment according to the trial protocol once clinical events such as ascites, variceal bleeding, overt hepatic encephalopathy, or hepatocellular carcinoma (HCC) occurred.

Outcome assessment

The primary endpoints were the composite of liver events and its individual components during the observational follow-up period, including variceal bleeding, ascites, overt hepatic encephalopathy, and HCC.

The secondary endpoint was the change in variceal grade on endoscopy after 96 weeks of treatment with FZHY plus entecavir or entecavir alone. Variceal bleeding was identified by the presence of bleeding from esophageal or gastric varices, confirmed by endoscopy. Ascites was identified based on physical examination findings and validated by ultrasonography or paracentesis, but not by intraperitoneal fluid detectable exclusively by ultrasonography or the presence of ankle edema alone.[8] Overt hepatic encephalopathy was defined according to the West Haven criteria, with symptoms and signs ≥ grade II.[19] HCC was diagnosed on the basis of validated imaging criteria (contrast-enhanced magnetic resonance imaging or computed tomography) or liver biopsy.[20]

The grading of esophageal varices on endoscopy was based on the following criteria. Grade 1: straight, small-caliber varices (the largest diameter < 0.3 cm) without red color signs; Grade 2: small-caliber varices (the largest diameter < 0.3 cm) with red color signs, or moderately enlarged, tortuous varices (the largest diameter between 0.3 and 1 cm) without red color signs; Grade 3: moderately enlarged varices with red color signs (the diameter between 0.3 and 1 cm), or markedly enlarged varices (the largest diameter > 1 cm) with or without red color signs. Regression of varices was defined as a ≥1-grade decrease in esophageal variceal grade after treatment.[21] Endoscopic data were independently reviewed by two endoscopists who were blinded to the trial assignments. Any discrepant results were reevaluated by a third endoscopist to reach a final consensus.

Safety assessments

Vital signs, physical examinations, adverse events, concomitant medications, routine blood tests, and electrocardiograms were monitored.

Statistical analysis

Statistical analyses were performed using the modified intention-to-treat (mITT)/full analysis set (FAS) and per-protocol populations. The mITT/FAS included all randomized participants with available baseline data and at least one post-randomization visit. Continuous variables with a normal distribution are expressed as the mean ± standard deviation and were compared using the Student's t test. Non-normally distributed data are presented as the median (IQR), and comparisons between groups were performed using the Mann-Whitney U test. Categorical variables were compared using Fisher's exact test or the chi-square test. Multivariable Cox proportional hazards regression analysis was used to identify independent factors associated with liver-related composite endpoints. The log-rank test was used to compare the two study groups in terms of primary endpoints. Statistical analysis was performed using SPSS version 19.0 (IBM, New York, USA) and R version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-sided, with a 5% significance level.

Results

Baseline characteristics

Of the 374 patients screened for compensated HBV-related cirrhosis in the RCTs, 142 were excluded before randomization, and 232 patients underwent randomization (Fig. 1). The reasons for exclusion before randomization were as follows: 22 patients were not diagnosed with cirrhosis; 5 patients did not meet the age requirement; 9 patients had HBV DNA levels > 50 IU/mL; 27 patients had a Child-Pugh score ≥ 9; 25 patients declined to participate in the study; 14 patients refused to sign the informed consent form; 10 patients had incomplete laboratory data; 2 patients

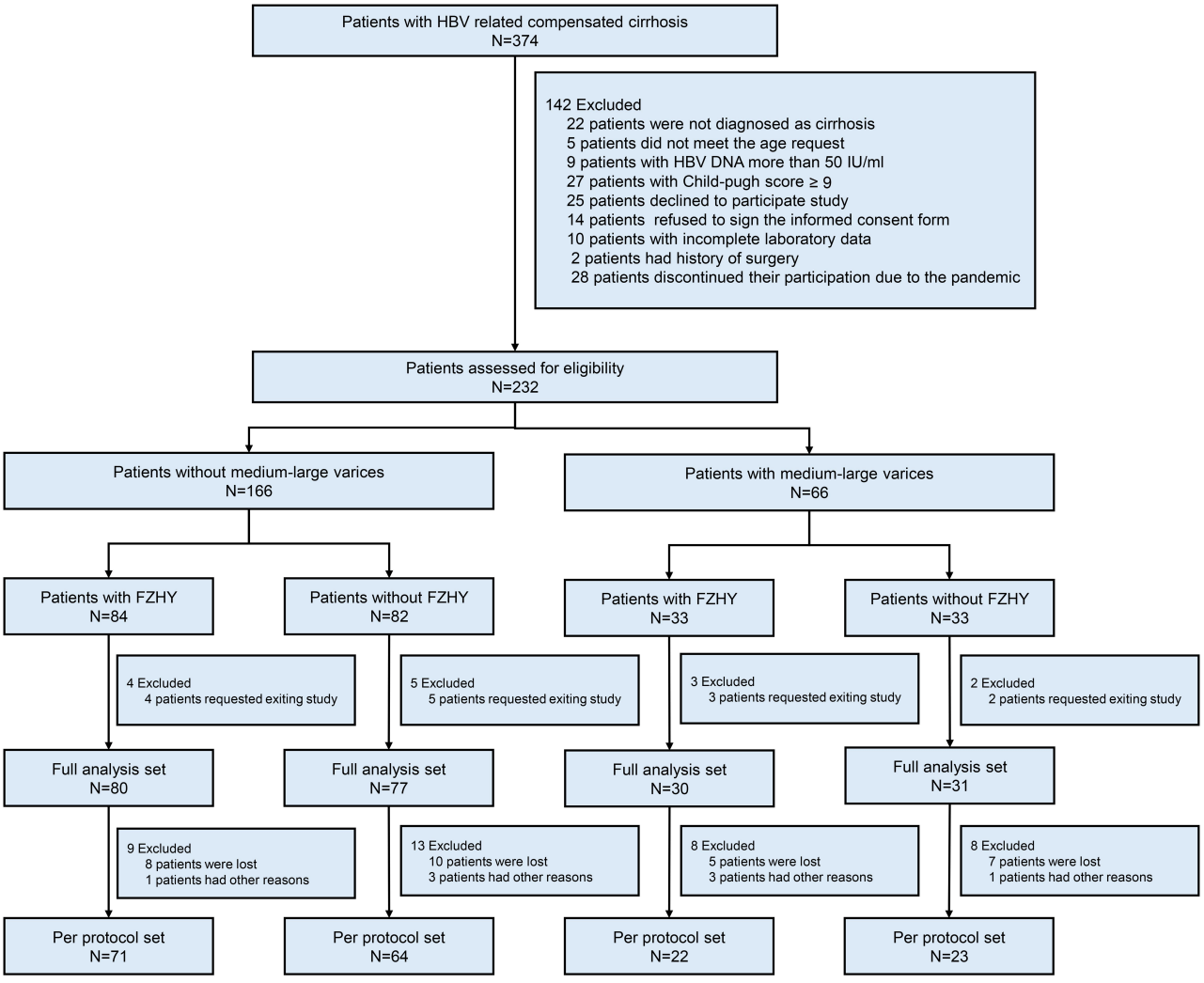

Fig. 1. Flow of participants. FZHY, Fuzheng Huayu; HBV, hepatitis B virus.

had a history of surgery due to lung tumor and bone fracture respectively; 28 patients discontinued their participation due to the pandemic. After randomization, 14 patients withdrew without any valid post-randomization efficacy assessment and were therefore excluded from the mITT/FAS (Fig. 1). Of the 218 patients who were finally included in the primary analysis, 108 participants were assigned to the entecavir group and 110 to the entecavir plus FZHY group. The median observational follow-up time was 23.1 months. The baseline characteristics of the participants are shown in Table 1. The mean age of the participants was 51.5 years, and 66.5% were male. Baseline characteristics were comparable between the two groups in both the full analysis set and the per-protocol set (Table 1, Supplementary Table. 1).

Primary outcome

In the primary analysis, liver events occurred less frequently in the FZHY group than in the control group in both the full analysis set (hazard ratio (HR) = 0.408 [0.187–0.892], $P = 0.020$) and the per-protocol set (HR = 0.383 [0.157–0.932], $P = 0.030$) (Fig. 2, Table 2). Importantly, among the individual components of liver events, the incidence of ascites was significantly lower in the FZHY group than in the control group (1.8% vs. 9.3%, $P = 0.016$). No significant differences were observed in the incidences of other complications, including variceal bleeding, overt hepatic encephalopathy, and HCC, between the FZHY and control groups (4.5% vs. 7.4%, $P = 0.372$; 0% vs. 0%, not applicable; 1.8% vs. 2.8%, $P = 0.636$, respectively).

Secondary outcomes

All participants in the full analysis set had evaluable baseline and follow-up endoscopic examinations, with no missing endoscopic data for the analysis of variceal regression. The rate of variceal regression was significantly higher in the FZHY group than in the control group (27.3% *vs*. 10.2%, $P < 0.001$) (Table 2).

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Table 1. Baseline characteristics in the full analysis set

	Patients with FZHY n = 110	Patients without FZHY n = 108	*P*-value
Age, year, mean ± SD	51.0 ± 9.0	52.0 ± 8.8	0.405
Sex, n, %			0.962
Male	73 (66.4)	72 (66.7)	
Female	37 (33.6)	36 (33.3)	
Platelets, 10^9/L, median (IQR)	97.0 (62.5, 139.8)	98.0 (58.0, 140.0)	0.901*
alanine Aminotransferase (ALT), IU/L, median (IQR)	27.0 (19.0, 36.0)	29.0 (22.0, 38.0)	0.160*
Aspartate aminotransferase (AST), IU/L, median (IQR)	29.0 (24.0, 37.0)	31.0 (25.0, 41.0)	0.063*
Total bilirubin, μmol/L, median (IQR)	18.6 (15.0, 25.0)	19.7 (14.3, 26.9)	0.629*
Albumin, g/L, median (IQR)	44.0 (40.9, 46.0)	44.0 (40.0, 46.0)	0.960*
Prothrombin time, s, mean ± SD	13.2 ± 1.6	13.4 ± 1.8	0.252
Liver stiffness measurement, kPa, median (IQR)	13.1 (10.1, 16.8)	13.1 (9.9,16.8)	0.700*
Child-Pugh, n, %			0.205
A	99 (90.0)	91 (84.3)	
B	11 (10.0)	17 (15.7)	
Varices grade, n, %			0.814
Non-medium-large	81 (73.6)	78 (72.2)	
Medium-large	29 (26.4)	30 (27.8)	
Use of carvedilol, n (%)	29 (26.4)	30 (27.8)	0.814

*ALT, AST, platelets, total bilirubin, albumin, and liver stiffness measurement were non-normally distributed and are shown as median (IQR) and compared using the Mann-Whitney U test. Other normally distributed continuous data are presented as mean ± SD and were compared using the independent t test. Categorical variables were assessed using the chi-square test. ALT, alanine aminotransferase; AST, aspartate aminotransferase; FZHY, Fuzheng Huayu; IQR, interquartile range; SD, standard deviation.

Multivariable analysis

In this study, all clinically meaningful confounding factors and variables with potential impacts on portal hypertension-related composite endpoints were included in the multivariable Cox regression model. These variables included baseline demographic characteristics, laboratory indicators, liver stiffness, and esophageal variceal grade.

Two predictors were identified by multivariable analysis of the occurrence of total liver events: FZHY treatment [HR (95% confidence interval (CI)), 0.362 (0.159–0.828) in the full analysis set and 0.383 (0.151–0.973) in the per-protocol set] and medium-to-large varices [HR (95% CI), 4.796 (1.980–11.613) in the full analysis set and 5.117 (1.733–14.836) in the per-protocol set]. Other factors, such as age, sex, platelet count, alanine aminotransferase, aspartate aminotransferase, total bilirubin, albumin, prothrombin time, liver stiffness measurement, and Child-Pugh class, were not significantly associated with the occurrence of overall liver-related events (Table 3, Supplementary Table. 2).

Stratification analysis

We performed separate multivariable Cox proportional hazards regression analyses stratified by esophageal variceal severity (mild vs. medium-to-large) at baseline and adjusted for age, prothrombin time (PT), liver stiffness measurement (LSM), albumin (ALB), total bilirubin (TB), alanine aminotransferase (ALT), aspartate aminotransferase-to-platelet ratio index (APRI). The results were consistent with the primary analysis. In patients with mild varices, combination therapy was not significantly associated with liver-related composite endpoints (HR = 0.905, 95% CI, 0.232–3.525, P = 0.885 in the full analysis set and HR = 0.767, 95% CI, 0.155-3.799, P = 0.745 in the per protocol set). In contrast, among patients with medium-to-large varices, combination therapy was significantly associated with a lower risk of liver-related events (HR = 0.190, 95% CI, 0.057–0.634, P = 0.007 in the full analysis set and HR = 0.162, 95% CI, 0.041–0.646, P = 0.010 in the per protocol set). Detailed stratified results are presented in Table 4 and Supplementary Table. 3.

Adverse events

During the study period, nonfatal adverse events occurred in 10 patients (9.1%) in the FZHY group and 8 patients (7.4%) in the control group (P = 0.652). Adverse events in the FZHY group included 2 cases of dyslipidemia, 3 cases of hyperglycemia, 2 cases of leukocytosis, and 3 cases of renal dysfunction. Adverse events in the control group included 1 case of dyslipidemia, 3 cases of hyperglycemia, 3 cases of renal dysfunction, and 1 case of elevated C-reactive protein. No severe adverse events were observed in either the treatment group or the control group, and no

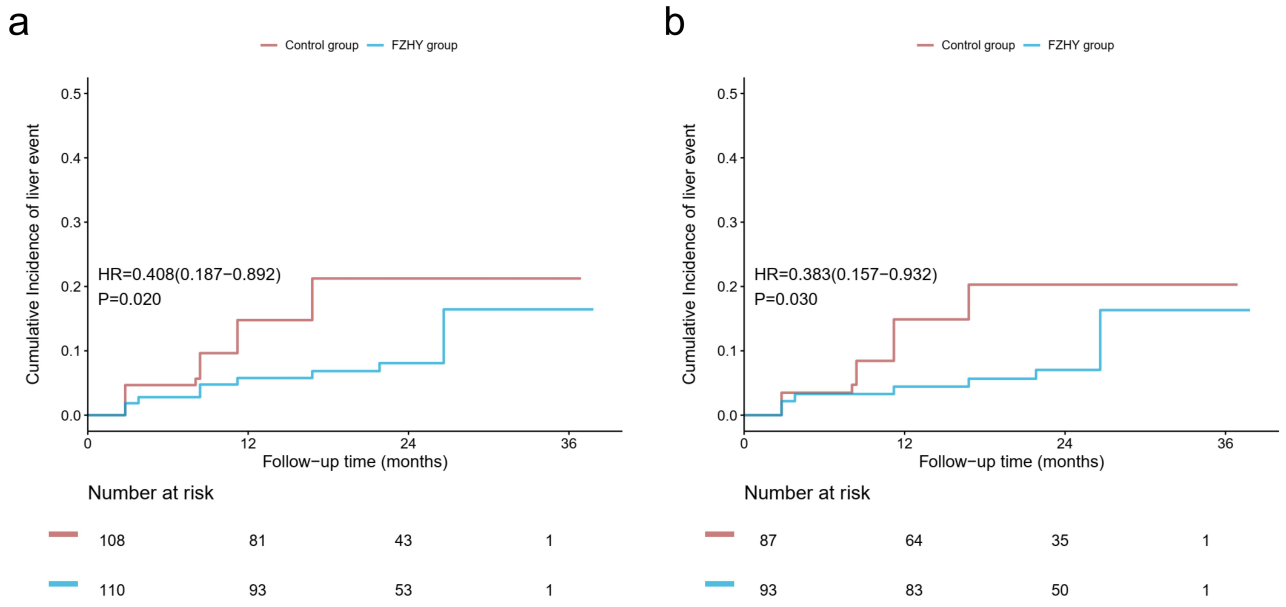

Fig. 2. Occurrence of total liver events during the observational follow-up period of up to 36 months according to treatment group. a: Full analysis set; b: per-protocol set. FZHY, Fuzheng Huayu; HR, hazard ratio.

Table 2. Occurrence of liver events

	Patients with FZHY n = 110	Patients without FZHY n = 108	*P*-value
Total event, n, %	9 (8.2)	21 (19.4)	0.016
Variceal bleeding, n, %	5 (4.5)	8 (7.4)	0.372
Ascites, n, %	2 (1.8)	10 (9.3)	0.016
hepatic encephalopathy, n, %	0 (0)	0 (0)	–
hepatocellular carcinoma, n, %	2 (1.8)	3 (2.8)	0.636
Variceal regression	30 (27.3)	11 (10.2)	<0.001

FZHY, Fuzheng Huayu.

participants withdrew due to adverse reactions in either group.

Discussion

In this clinical study of Chinese patients with HBV-related compensated cirrhosis, the Chinese traditional medicine FZHY, as an adjunctive therapy to antiviral entecavir, significantly reduced the risk of portal hypertension-related decompensation, specifically cirrhotic ascites, while no significant differences were observed in other liver events, including variceal bleeding, overt hepatic encephalopathy, HCC, or adverse events. In addition, FZHY treatment and variceal grade were independent predictors of the occurrence of total liver events. In stratified analyses, a statistically significant association was observed in patients with medium-to-large esophageal varices, rather than those with mild varices. However, these findings should be interpreted cautiously because a formal interaction test was not performed.

FZHY was originally designed to treat hepatic fibrosis. *In vivo* and *in vitro* studies have revealed the mechanisms by which FZHY treats hepatic fibrosis: (1) protecting hepatocytes. It could improve liver function, decrease hepatic oxidative stress, and inhibit hepatocyte apoptosis; (2) inhibiting hepatic stellate cell (HSC) activation. It could inhibit PDGF-BB-stimulated proliferation of HSCs, inhibit collagen secretion in a dose-dependent manner, particularly type I collagen secretion and gene expression, and decrease TGF-β1 expression in activated HSCs; and (3) decreasing the concentration of endothelin-1.[17,22] Through its antifibrotic effects and maintenance of cardiac output, FZHY could enhance hepatic blood circulation by increasing hepatic blood flow volume and velocity, thus lowering the risk of portal hypertension in patients with liver cirrhosis.[17] Consistently, our study showed a higher rate of variceal regression with FZHY, with variceal severity serving as an endoscopic marker related to portal hypertension severity. Furthermore, FZHY lowers intrahepatic

Table 3. Multivariable analysis of the occurrence of total liver events in the full analysis set

Variable	HR	*P*-value
Age, year, mean ± SD	0.981 (0.940-1.024)	0.378
Sex, n, %		0.687
Male	Reference	
Female	1.204 (0.487-2.976)	
Platelets, 10^9/L	0.994 (0.984-1.004)	0.255
alanine aminotransferase, IU/L	1.010 (0.965-1.058)	0.659
aspartate aminotransferase, IU/L	0.961 (0.917-1.007)	0.093
Total bilirubin, μmol/L,	0.978 (0.931-1.028)	0.384
Albumin, g/L	0.981 (0.900-1.070)	0.667
Prothrombin time, s	1.090 (0.803-1.480)	0.580
Liver stiffness measurement, kPa	1.014 (0.961-1.070)	0.612
Child-Pugh, n, %		0.503
A	Reference	
B	1.593 (0.408-6.224)	
Treatment		0.012
Without FZHY	Reference	
With FZHY	0.362 (0.159-0.828)	
Varices grade		0.001
Mild esophageal varices	Reference	
Medium-large varices	4.796 (1.980-11.613)	

FZHY, Fuzheng Huayu; HR, hazard ratio; SD, standard deviation.

Table 4. Stratified multivariable analysis of total liver events by variceal severity in the full analysis set

Subgroup	Treatment	Adjusted HR (95% CI)	*P*-value
Mild esophageal varices	Patients without FZHY	1.00	–
	Patients with FZHY	0.905 (0.232-3.525)	0.885
Medium-large esophageal varices	Patients without FZHY	1.00	–
	Patients with FZHY	0.190 (0.057-0.634)	0.007

The analysis was adjusted for age, PT, LSM, ALB, TB, ALT, and APRI. CI, confidence interval; FZHY, Fuzheng Huayu; HR, hazard ratio; PT, prothrombin time; LSM, liver stiffness measurement; ALB, albumin; TB, total bilirubin; ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index.

resistance via antifibrotic structural improvements, whereas NSBBs reduce portal pressure by decreasing portal venous blood flow, indicating entirely distinct mechanisms.[5]

Beyond these observations, the most notable finding of this study was that FZHY reduced the risk of decompensation, primarily by lowering the incidence of ascites, the most common and clinically significant decompensating event, which was attributed to its effects on regression of liver fibrosis and improvement of hepatic blood flow and portal hypertension. Interestingly, there were no statistically significant differences between the FZHY and control groups in the other decompensation events. Similarly, a previous study reported that, in patients with compensated cirrhosis and CSPH, long-term treatment with NSBBs decreased portal pressure and improved decompensation-free survival, mainly by decreasing the incidence of ascites rather than variceal bleeding or hepatic encephalopathy.[8] We speculate that this may be because most patients presented with ascites as their first episode of clinical decompensation.[23]

Our results seem to contrast with a previous retrospective study showing the effectiveness of FZHY in reducing the incidence of HCC in patients with HBV-related cirrhosis, independent of Child-Pugh classification.[24] We attribute the discrepant findings, at least in part, to the relatively longer follow-up period in the previous study (5 years vs. a maximum observational follow-up of

approximately 36 months in our study) and its higher baseline HCC risk resulting from the inclusion of a proportion of patients with decompensated cirrhosis. In addition, another small-sample randomized controlled study indicated that FZHY was useful in preventing esophageal variceal bleeding in patients with liver cirrhosis and varices.[17] In contrast, no significant difference in variceal bleeding was observed in the present study. The fact that most patients enrolled in this study were at an earlier stage with no or small varices might explain this finding.

A key strength of this study is that it addresses a critical gap by being the first to evaluate the efficacy of FZHY in preventing the progression of portal hypertension-related complications. We confirmed the benefit of FZHY in a cohort of patients with compensated cirrhosis, with a relatively long follow-up period. The findings observed for the primary and secondary outcomes were generally consistent and favored FZHY. In addition, similar baseline characteristics among groups minimized selection bias.

This study had several limitations. First, data for this study were pooled from two parallel RCTs that enrolled patients with distinct baseline characteristics—specifically, those with no or small varices or with medium-to-large varices. This design may have introduced potential selection bias. However, the primary and secondary endpoints were uniform across these studies. Second, hepatic venous pressure gradient, the gold standard for assessing portal pressure, was not routinely measured in this study because it is invasive and costly; instead, the severity of varices observed on endoscopy was used as a surrogate marker.[21] This represents a limitation of the study, but the endoscopy data were centrally reviewed by two staff endoscopists who were blinded to group assignment. Third, the overall number of liver events observed in this study was relatively low, which may limit the statistical power to detect differences in specific components of the composite endpoint and the stability of the multivariable estimates. Therefore, our findings regarding the reduction in decompensation events should be interpreted with caution, and further validation in larger cohorts with longer follow-up is warranted.

Conclusions

This post hoc analysis of two RCTs suggests that adjunctive FZHY treatment was associated with fewer liver-related events, particularly ascites, and a higher rate of variceal regression in patients with compensated HBV-related cirrhosis. These findings warrant confirmation in adequately powered prospective studies.

Supporting information

Supplementary material for this article is available at https://doi.org/10.14218/JTG.2026.00019.

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Conflict of interest

None declared.

Author contributions

Study design (ChL, JL), revision of the manuscript (XQ), data analysis (CL), writing of the manuscript (YG, LD), guarantors of the study (ChL, JL). All authors contributed to data acquisition, review, and approval of the manuscript.

Ethical statement

Ethical approval was obtained from the Ethics Committee of Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine (approval No. 2017-560-43). From October 2017 to March 2021, the study was performed in accordance with the ethical standards of the Declaration of Helsinki (as revised in 2024), and the principles of Good Clinical Practice. Written informed consent was obtained from each participant.

Data sharing statement

All data relevant to the study are included in the article or provided as supplementary information. Additional supporting data are available from the corresponding author upon request.

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