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Original Article

Beneficial Effects of Traditional Chinese Medicine Fuzheng Huayu on the Occurrence of Hepatocellular Carcinoma in Patients with Compensated Chronic Hepatitis B Cirrhosis Receiving Entecavir: A Multicenter Retrospective Cohort Study

Haina Fan[1#], Shujuan Lei[1#], Zhimin Zhao[1], Yan Huang[2], Hui Wang[2], Xudong Liu[3], Xiaodong Li[4], Min Xu[5], Wei Zhang[6], Kewei Sun[7], Huichun Xing[8], Yang Mei[9], Jiaquan Huang[10], Chuanwu Zhu[11], Kejun Zhang[12], Yali Zong[13], Xizhong Shen[14], Qing Xie[2*] and Chenghai Liu[1*]

[1]Institute of Liver Diseases, Shanghai Key Laboratory of Traditional Chinese Clinical Medicine, Key Laboratory of Liver and Kidney Diseases (Ministry of Education), Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China; [2]Department of Infectious Diseases, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [3]Department of Infectious Diseases, Ruikang Hospital Affiliated to Guangxi University of Chinese Medicine, Nanning, Guangxi, China; [4]Institute of Liver Diseases, Hubei Provincial Hospital of Traditional Chinese Medicine, Wuhan, Hubei, China; [5]Department of Infectious Diseases, Huaian Fourth People's Hospital, Huai'an, Jiangsu, China; [6]Institute of Liver Diseases, Shijiazhuang Fifth Hospital, Shijiazhuang, Hebei, China; [7]Department of Liver Diseases, The First Hospital of Hunan University of Chinese Medicine, Changsha, Hunan, China; [8]Center of Hepatology, Capital Medical University Affiliated Beijing Ditan Hospital, Beijing, China; [9]Department of Hepatology, The Fifth People's Hospital of Anyang, Anyang, Henan, China; [10]Department and Institute of Infectious Disease, Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology, Wuhan, Hubei, China; [11]Department of Hepatology, The Fifth People's Hospital of Suzhou, Suzhou, Jiangsu, China; [12]Department of Gastroenterology, The First People's Hospital of Jingmen, Jingmen, Hubei, China; [13]Department of Integrated Traditional and Western Medicine, The Ninth Hospital of Nanchang, Nanchang, Jiangxi, China; [14]Department of Gastroenterology, Zhongshan Hospital, Fudan University, Shanghai, China

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Abstract

Background and Aims: The application of antifibrotic drugs to treat patients with chronic liver diseases who are receiving antiviral therapies for hepatocellular carcinoma (HCC) has not been established. Here, we aimed to assess the impact of the Traditional Chinese Medicine Fuzheng Huayu (FZHY) on the occurrence of HCC in patients with hepatitis B virus-related compensated cirrhosis receiving the antiviral drug entecavir (ETV). ***Methods:*** A multicenter retrospective cohort study was performed. Compensated liver cirrhosis patients were divided into the ETV+FZHY group or the ETV group according to treatment. The cumulative incidence of HCC was analyzed using Kaplan-Meier and log-rank tests. Propensity score matching was used for confounding factors. Stratified analysis and Cox regression were used to determine the effects of FZHY on the occurrence of HCC and liver function decompensation. ***Results:*** Out of 910 chronic hepatitis B patients, 458 were in the ETV+FZHY group and 452 were in the ETV group. After propensity score matching, the 5-year cumulative incidence of HCC was 9.8% in the ETV+FZHY group and 21.8% in the ETV group ($p<0.01$). The adjusted hazard ratio for HCC was 0.216 (0.108, 0.432) when FZHY treatment was >36 months. Age, diabetes, alanine aminotransferase, γ-glutamyl transpeptidase, albumin, hepatitis B e-antigen, and fibrosis 4 score were associated with the occurrence of HCC. FZHY decreased the risk of HCC in patients aged >45 years with a hepatitis B virus DNA level of ≥2,000 IU/l. ***Conclusion:*** Adjunctive FZHY treatment reduced HCC occurrence in patients with hepatitis B virus cirrhosis who were treated with ETV, possibly due to the antifibrotic properties of FZHY.

Keywords: Entecavir; Fuzheng Huayu; Hepatitis B virus; Cirrhosis; Hepatocellular carcinoma; Traditional Chinese Medicine.

Abbreviations: AFP, alpha-fetoprotein; Alb, albumin; ALT, alanine aminotransferase; APRI, AST/PLT ratio index; AST, aspartate aminotransferase; CHB, chronic hepatitis B; CI, confidence interval; Cr, creatinine; CT, computed tomography; ETV, entecavir; FIB-4, Fibrosis 4 Score; FZHY, Fuzheng Huayu tablets; GGT, γ-glutamyl transpeptidase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HGB, hemoglobin; INR, international normalized ratio; IQR, interquartile range; KM, Kaplan-Meier; LSM, liver stiffness measurement; MRI, magnetic resonance imaging; NAs, nucleos(t)ide analogues; PHT, portal hypertension; PLT, platelet; PSM, propensity score matching; RCT, randomized clinical trial; TBil, total bilirubin; TCM, Traditional Chinese Medicine; ULN, upper limit of normal; VR, virological response; WBC, white blood count.

[#]Contributed equally to this work.

[*]**Correspondence to:** Chenghai Liu, Institute of Liver Diseases, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, No.528 Zhangheng Road, Pudong New District, Shanghai 201203, China. ORCID: https://orcid.org/0000-0002-1696-6008. Tel/Fax: +86-21-53821650, E-mail: chenghailiu@hotmail.com; Qing Xie, Department of Infectious Diseases, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, No.197 Ruijin Road Number Two, Huangpu District, Shanghai 200025, China. ORCID: https://orcid.org/0000-0002-3298-1072. Tel/Fax: +86-21-64370045, E-mail: xieqingrjh@163.com

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Introduction

Hepatocellular carcinoma (HCC) is a major cause of cancer-related deaths worldwide.[1] In recent decades there has been substantial progress in understanding the epidemiology, risk factors, and molecular mechanisms of HCC, as well as in prevention, surveillance, diagnosis, and treatment.

Hepatitis B virus (HBV) is a significant risk factor for HCC. Elimination of HBV infection by vaccinations or suppression of HBV replication with antiviral drugs such as interferon or nucleoside analogues (NAs) can substantially reduce the occurrence of HCC.[2] However, patients with a virologic response to NAs still experience a high occurrence of HCC compared to individuals with inactive chronic hepatitis B (CHB).[3] Thus, antiviral therapy alone in patients with chronic hepatitis B does not eliminate the development of HCC,[4] necessitating alternative prevention approaches.

Liver fibrosis and cirrhosis are crucial risk factors for the development of HCC. Approximately 70% to 80% of HCC patients have cirrhosis. The risk of HCC is nearly 10 times higher in individuals with moderate liver fibrosis (F3-4) compared to those with early or no fibrosis (F0-F2).[5] In Asia, the annual incidence of liver cancer in HBV carriers without cirrhosis is approximately 0.5 to 1%, whereas it rises significantly to 3 to 6% for patients with cirrhosis.[6]

Traditional Chinese Medicine (TCM) has a rich history in treating chronic liver diseases and has led to the development of several antifibrotic products over the years. In the treatment of HCC, certain herbal products have shown potential benefits.[7,8] In particular, antifibrotic herbal products have shown efficacy in reducing HCC occurrence among patients with CHB.[9,10]

A previous meta-analysis demonstrated the clinical efficacy of the herbal product Fuzheng Huayu (FZHY) in terms of its antifibrosis effects,[11] and also demonstrated benefits when paired with liver biopsies to treat patients with CHB.[12] FZHY has also been shown to significantly reduce the 5-year cumulative incidence of HCC in patients with hepatitis B cirrhosis.[10] However, these prior studies have limitations in terms of heterogeneous participants, including varying degrees of liver fibrosis, and different antiviral drugs such as entecavir (ETV), adefovir, and others. The primary endpoints of these studies mainly focused on varying occurrences of HCC (Supplementary Table 1), and the role of antifibrotic treatments on the occurrence of HCC and degree of fibrosis (compensated or decompensated cirrhosis) remains unclear. Thus, we designed a multicenter large sample cohort study to determine the occurrence of HCC for patients with compensated CHB cirrhosis receiving either the antiviral ETV alone or ETV plus the antifibrotic TCM FZHY.

Methods

Study design and patients

This multicenter retrospective cohort study involved 20 participating sites nationwide in China during a period of eight years from January 2013 to December 2021. The inclusion criteria were as follows: (1) patients aged between 18 and 80 years old, (2) positive HBsAg for more than 6 months with no prior ETV treatment, and (3) compensated liver cirrhosis.[13] The exclusion criteria were: (1) decompensated cirrhosis, (2) patients who had HCC, liver transplantation, or stem cell transplantation, (3) patients treated with ETV for less than 12 months or with interferon application for more than 4 weeks, (4) patients who experienced HCC or decompensation events within 12 months after treatment, and (5) missing or incorrect key data, including important medical history, main biochemical indicators, HBV DNA, HBeAg, and HBeAb.

The enrolled patients were divided into two groups based on their drug history in the Hospital Information System: ETV+FZHY and ETV alone. This study adhered to the Helsinki Declaration of 1975 and received approval from the Medical Ethics Committee of Shuguang Hospital.

Diagnosis criteria

Liver cirrhosis: Pathology: Cirrhosis was confirmed through assessing the Ishak stage, specifically F5 or F6.

Imaging: Abdominal ultrasound, liver stiffness measurement (LSM), abdominal CT, or MRI were used to indicate cirrhosis or portal hypertension.

Fibroscan: For patients with normal total bilirubin (TBil) and alanine aminotransferase (ALT) ranged from ULN-5×ULN (ULN=40 U/L), a Fibroscan result of ≥17.0 kPa was indicative of cirrhosis. For those with normal TBil and ALT, a value of ≥12.0 kPa was suggestive of cirrhosis.

In cases where pathology, endoscopy, and image data were unavailable, a diagnosis of cirrhosis was made if at least two of the following criteria were met: (1) platelet count (PLT) $<100\times10^9$ cells/L without any other identifiable causes; (2) serum albumin (Alb) <35.0 g/L; (3) international normalized ratio (INR) >1.3 or prolonged by more than 3 seconds; and (4) AST/PLT ratio index (APRI) >2.

HCC: An HCC diagnosis was based on at least one of the following criteria: (1) HCC confirmed through pathological examination of a tissue sample, or (2) liver/abdominal MRI/CT scan suggestive of HCC.[14]

Decompensation events: Decompensation events included pleural fluid or ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome. These events were further divided into two categories: portal hypertension-related events (including pleural fluid or ascites and variceal bleeding) and other hepatic events.

Modified PAGE-B (mPAGE-B) score[15]

The mPAGE-B score, which is estimated according to PLT counts, age, and gender, was used to define HCC risks among CHB patients receiving antiviral treatment. For mPAGE-B scores ≤8, the patients were considered at low-risk, for 9–12 scores, at medium-risk; and for scores ≥13, at high-risk.

Treatment and follow-up

Entecavir was given orally at 0.5 mg once a day, and FZHY tablets (details of the quality control can be found in the supplementary material) were given orally at 1.6 g three times a day. Clinical information from patients was collected at three time points: the initial antiviral treatment (baseline), one year after antiviral treatment, and the final follow-up of endpoint events including the occurrence of HCC or decompensation events.

Outcomes and endpoints

The primary endpoint was the 5-year cumulative incidence

of HCC. The secondary endpoint was the 5-year cumulative incidence of decompensation events.

Sample size calculation

In this study, we anticipated that the combination therapy of ETV and FZHY would decrease the 5-year occurrence of HCC by 25% compared to ETV alone, resulting in an expected incidence rate of 10.4%.[10] We used the reference value from the study by Wong et al. who reported a 13.8% cumulative 5-year incidence of HCC in patients with compensated hepatitis B cirrhosis receiving ETV intervention.[16]

To determine the required sample size, a 1:1 ratio was used for cases in both groups of ETV+FZHY and ETV alone. The statistical efficacy was set at 0.8. The sample size calculation was based on the 5-year cumulative event rate in both groups, employing the Log rank test, which resulted in a minimum sample size of 417 participants in each group.

Statistical analysis

Values were expressed as means±SD or number and percentage (%). Normally distributed continuous variables were compared using the t-test, while the Mann-Whitney U test was utilized for non-normally distributed data. For categorical data, the Chi-square test and Fisher's exact test were employed.

The cumulative incidence of HCC is presented using a Kaplan-Meier (KM) curve and tested using the log-rank test. Propensity score matching (PSM) was employed for the correction of confounding factors. The indicators considered in the matching process included gender, age, HBV DNA, HBeAg, HBeAb, ALT, aspartate aminotransferase (AST), TBiL, Alb, γ-glutamyl transpeptidase (GGT), PLT, creatinine (Cr) and alpha-fetoprotein (AFP). A 1:1 ratio was used for PSM, and the caliper range was set at 0.2.

Subgroup analysis involved comparing the 5-year cumulative incidence of HCC and decompensation events between the ETV and ETV+FZHY interventions, based on the duration of therapy and the mPAGE-B risk score. Cox regression analysis was performed to assess the risk factors for HCC between the ETV+FZHY and ETV groups. The crude hazard ratio (HR) and adjusted HR (aHR), along with their corresponding 95% confidence intervals (CI), were computed and interpreted accordingly. APRI and FIB-4 comparisons at different time points were analyzed using a two-way repeated-measures ANOVA (taking into account time and treatment modality). *p*-values of <0.05 were considered significant. All statistical analyses were conducted using SAS 9.4 and R data (version 4.1.3) software.

Results

Baseline characteristics of study population

A total of 1,774 patients from 20 centers nationwide were initially selected. A cohort of 910 patients was finally enrolled in the study according to the inclusion criteria. From this cohort, 458 patients received ETV+FZHY and 452 received ETV alone (Fig. 1). In this study, 512 patients were diagnosed with liver cirrhosis according to liver histology (pathology), and 398 patients were diagnosed based on images, biochemical parameters, etc. The median age was 50 years in the ETV+FZHY group and 45 years in the ETV group ($p<0.01$). There were 351 (76.8%) males in the ETV+FZHY group and 328 (72.5%) males in the ETV group ($p=0.095$). The median follow-up was 39 months.

At baseline, patients in the ETV+FZHY group exhibited lower levels of ALT, AST, and TBil, and higher levels of PLT and Alb compared to those in the ETV group ($p<0.05$) (Table 1). The prevalence of a family history of HCC, CHB and alcohol consumption was significantly higher in the ETV+FZHY group. Furthermore, there was a lower rate of diabetes at baseline in the ETV+FZHY group compared to the ETV group (both $p<0.01$).

After PSM, there were 231 patients in each group, and the baseline characteristics were comparable between the two groups (Table 1).

Primary endpoint

Effect of ETV+FZHY on the cumulative incidence of HCC: Before applying PSM, a total of 24 patients (5.2%) developed HCC in the ETV+FZHY group, while 91 patients (20.1%) developed HCC in the control group. Following PSM, the 3-year cumulative incidence of HCC was 3.3% and the 5-year cumulative incidence was 9.8% in the ETV+FZHY group. The cumulative incidence of HCC in the ETV group was 9.2% at 3 years and 21.8% at 5 years. These findings indicate that the application of ETV+FZHY therapy resulted in a lower cumulative incidence of HCC, regardless of whether PSM was applied.

There was a significant reduction in HCC occurrence in the ETV+FZHY group as evidenced by the KM survival analysis (Fig. 2). The cumulative incidence of HCC was significantly lower in the ETV+FZHY group ($p<0.01$) regardless of whether PSM was applied, suggesting the beneficial effect of ETV+FZHY therapy for reducing the risk of HCC development.

We divided the ETV+FZHY group into three subgroups based on the duration of FZHY usage: 6–12 months, 12–36 months, and >36 months. When the duration of FZHY usage was >12 months, the aHRs were 0.194 (95% CI 0.1–0.375, $p<0.01$) and 0.216 (95% CI 0.108–0.432, $p<0.01$) for the different time intervals, indicating stronger protective effects of FZHY on HCC occurrence when used for longer durations (Table 2 and Fig. 3). PSM analysis suggested that a duration of FZHY usage of >12 months was associated with a significant reduction in the occurrence of HCC (Fig. 3).

Based on mPAGE-B scores, the initial cohort was divided into three groups: low-risk (n=144), medium-risk (n=438) and high-risk (n=328). The cumulative incidence of HCC in the FZHY group decreased significantly in both the medium-risk and high-risk groups (both $p<0.05$, Fig. 4A–C). After PSM, the cumulative incidence of HCC in the FZHY group decreased significantly in the medium-risk group ($p=0.002$), but there was no significant benefit in the low-risk and high-risk groups after PSM (Fig. 4D–E).

Secondary endpoint

Effect of ETV+FZHY on the cumulative incidence of hepatic events: Before PSM, the ETV group had 13 decompensation events (excluding HCC) with a prevalence of 2.8%, while the ETV+FZHY group had 12 events (2.5%). In the ETV group, the decompensation events included upper gastrointestinal bleeding (n=5), spontaneous peritonitis (n=1), and ascites (n=7). Similarly, in the ETV+FZHY group, the decompensation events included upper gastrointestinal bleeding (n=5), and ascites (n=7). After PSM, a total of 11 PHT-related events were observed among all participants, with seven cases in the ETV group and four cases in the ETV+FZHY group.

The results of the KM analysis demonstrated that the cumulative incidence of PHT-related events over the 5-year follow-up was lower in the ETV+FZHY group compared to the ETV group. After PSM, the 5-year cumulative incidence of PHT-related events was 10.41% in the ETV group and 2.37%

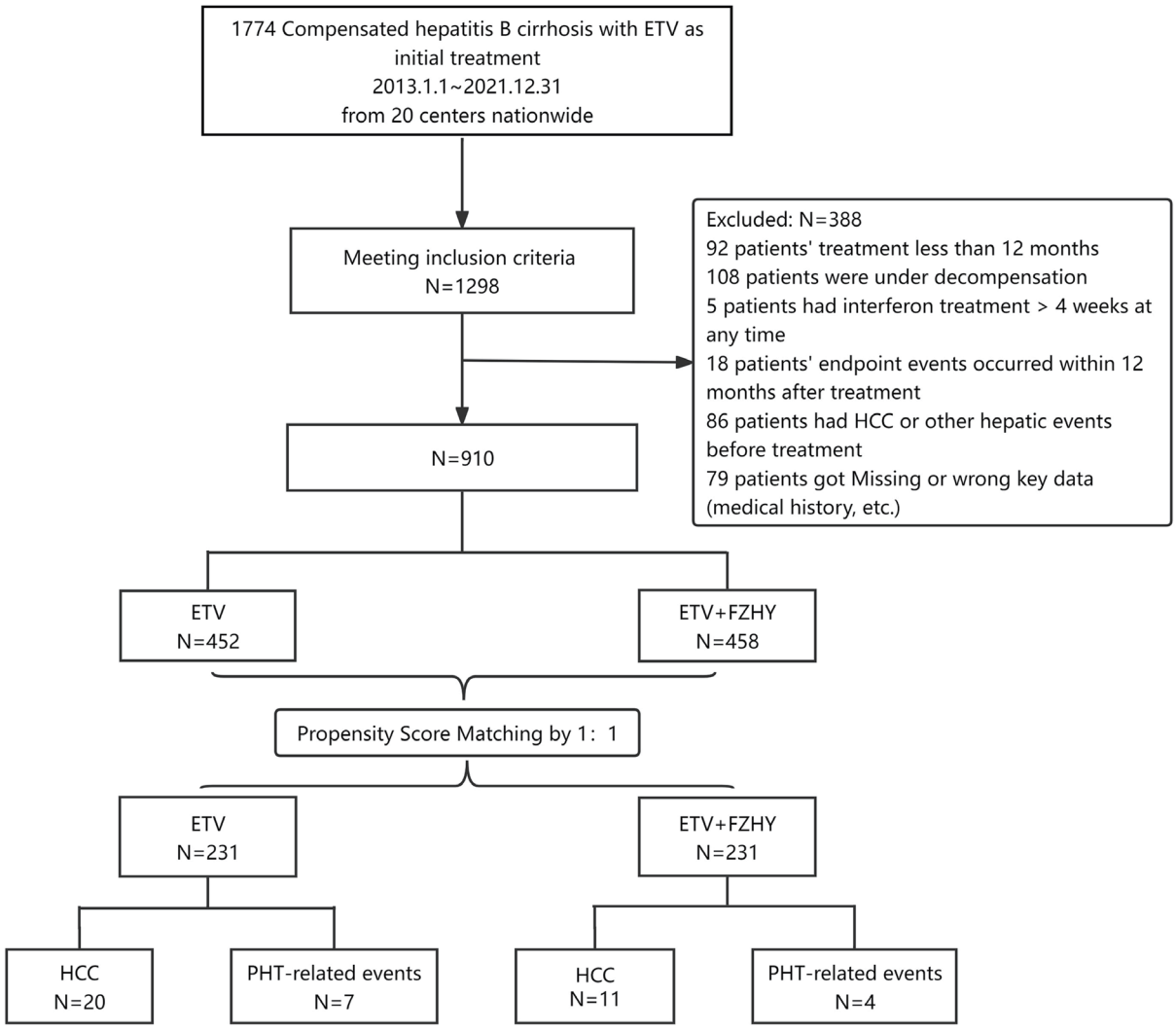

Fig. 1. Flowchart of patients with compensated CHB cirrhosis receiving in ETV+FZHY or ETV alone. CHB, chronic hepatitis B; ETV, entecavir; HCC, hepatocellular carcinoma; FZHY, Fuzheng Huayu tablets; PHT, portal hypertension.

in the ETV+FZHY group (p=0.083, Fig. 5).

Risk factors of HCC in CHB cirrhosis

Analysis of the initial cohort before PSM using both univariate and multivariate Cox regression revealed that several clinical factors were associated with the occurrence of HCC (Table 3). Protective factors for HCC included age <45 years, absence of diabetes, GGT <64 IU/l, and negative HBeAg. Elevated levels of ALT (>40 IU/l), lower levels of Alb (<35 g/l), and an increase in the FIB-4 index were risk factors for HCC (Table 3).

Stratified analysis following PSM revealed a reduction in the 5-year cumulative incidence of HCC in the ETV+FZHY group. Among patients >45 years of age, the combination of FZHY showed a significant reduction in the cumulative incidence of HCC (HR 0.45, 95% CI 0.203–0.996, p=0.049). Similarly, among individuals with lower ALT levels (<40 IU/l), FZHY treatment also resulted in a decrease in HCC occurrence (HR 0.239, 95% CI 0.088–0.649, p=0.005). Individuals with HBV DNA levels ≥2,000 IU/ml also exhibited a lower hazard of HCC when receiving FZHY therapy (HR 0.37, 95% CI 0.147–0.934, p=0.035). Overall, the combined therapy of FZHY had the potential to reduce the cumulative risk for the progression of cirrhosis to HCC (Fig. 6).

Chemoprevention of HCC may rely on FZHY's antifibrosis properties

We collected and analyzed HBV DNA data at 3 temporal phases: baseline, 1 year after antiviral therapy, and the final visit. Virological response (VR) was defined as HBV DNA<100 IU/ml.[6] After PSM, the rates of HBV VR between the HCC and non-HCC groups in all treatments at 1-year and the final visit were 76.7%, 80% and 77.6%, 72.4% (p=0.909 and 0.367, Supplementary Table 3). The rates of VR in patients with HCC between the two treatment groups which received ETV or FZHY+ ETV after PSM were 80% and 63.6% (p=0.405, Supplementary Table 4), it suggested that FZHY's adjunctive effect on tumorigenesis in patients with cirrhosis was not associated with HBV DNA inhibition, but may be closer to its anti-fibrotic property.

Evaluation of the noninvasive indexes of fibrosis during follow-up between the two groups revealed that FIB-4 and

Table 1. Clinical characteristics of patients with compensated CHB cirrhosis receiving ETV+FZHY or ETV alone in a multicenter retrospective cohort study

Variables	Before PSM			After PSM		
	ETV+FZHY (N=458)	ETV (N=452)	*p* values	ETV+FZHY (N=231)	ETV (N=231)	*p* values
Age (year, mean±SD)	44.65±9.45	48.96±11.48	<0.01	45.04±8.5	45.95±10.01	0.402
Male/Female (n, %)	352/103 (76.8/23.2)	328/124 (72.5/27.5)	0.095	172/59 (74.4/25.6)	174 /57 (75.3/24.7)	0.83
WBC (×109/l, mean±SD)	4.97±1.65	4.97±1.71	0.879	5.02±1.82	4.98±1.63	0.783
HGB (g/l, mean±SD)	142.51±17.89	142.54±17.86	0.40	143±17.63	142.93±16.88	0.914
PLT (×109/l, mean±SD)	125.97±56.54	111.85±52.92	<0.01	120.92±55.92	117.7±50.71	0.736
ALT (IU/l, mean±SD)	52.78±54.8	73.07±132.28	<0.01	52.99±55.03	56.76±59.33	0.733
AST (IU/l, mean±SD)	47.46±48.16	65.45±103.24	<0.01	49.11±54.17	50.65±45.93	0.811
GGT (IU/l, mean±SD)	66.86±63.89	75.41±74.19	0.153	69.88±66.78	69.57±70.71	0.226
Alb (g/l, mean±SD)	42.58±5.66	40.1±6.02	<0.01	41.85±5.56	41.35±5.51	0.409
TBil (μmol/l, mean±SD)	16.89±16.14	24.36±29.97	<0.01	17.8±19.95	18.82±12.18	0.781
Cr (μmol/l, mean±SD)	69.71±13.98	70.62±15.68	0.643	69.95±13.73	70.79±16	0.5
AFP (ng/ml, mean±SD)	29.55±86.54	30.19±75.77	0.187	32.92±90.06	31.26±85.18	0.072
HBV DNA (log10 IU/ml, mean±SD)	4.76±1.83	4.87±1.64	0.374	4.67±1.86	4.63±1.77	0.814
HBeAg Positive (n, %)	176 (38.4)	172 (38)	0.907	103 (44.5)	99 (42.8)	0.708
Diabetes (n, %)	15 (3.2)	44 (9.7)	<0.01	9 (3.8)	10 (4.3)	0.815
Alcohol consumption (n, %)	54 (11.7)	32 (7)	0.015	12 (5.1)	11 (4.7)	0.831
Family history of HBV (n, %)	104 (22.7)	65 (14.3)	<0.01	33 (14.2)	33 (14.2)	1
Family history of HCC (n, %)	33 (7.3)	11 (2.4)	<0.01	8 (3.4)	5 (2.1)	0.399
LSM (kPa, mean±SD)	18.23±11.72	17.59±11.14	0.973	19.51±12.68	16.94±11.68	0.285

AFP, alpha fetoprotein; Alb, albumin; ALT, alanine aminotransferase, AST, aspartate aminotransferase; Cr, creatinine; ETV, entecaivr; FZHY, Fuzheng Huayu tablets; GGT, γ-glutamyl transpeptidase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HGB, hemoglobin; IQR, interquartile range; PLT, platelet; PSM, propensity score matching; TBil, total bilirubin; WBC, white blood count; LSM, liver stiffness measurement; CHB, chronic hepatitis B.

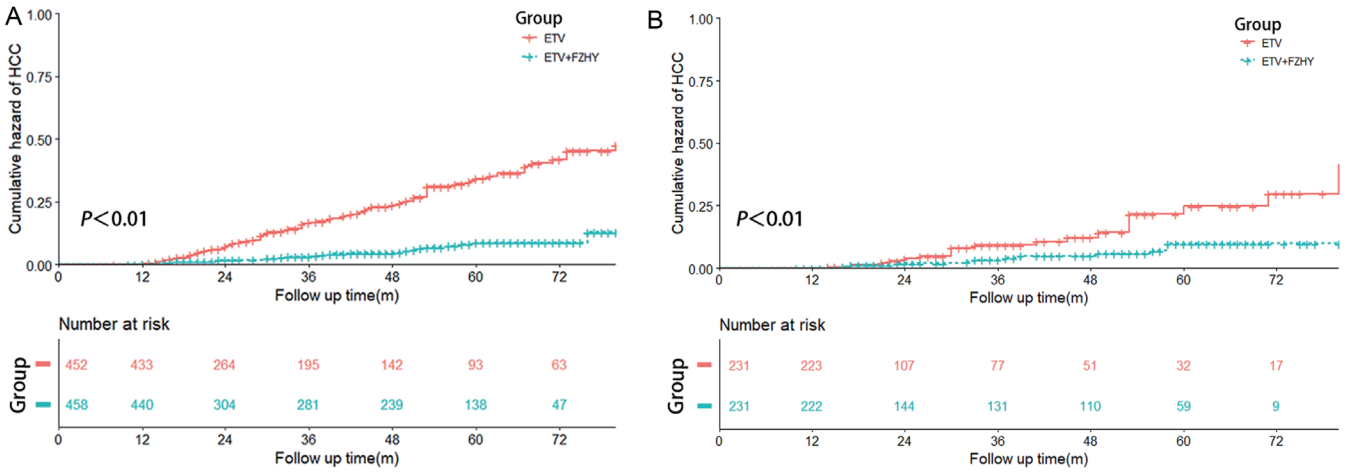

Fig. 2. The cumulative hazard of HCC in patients with compensated CHB cirrhosis receiving ETV+FZHY or ETV alone before (A) and after (B) PSM. ETV, entecavir; FZHY, Fuzheng Huayu tablets; HCC, hepatocellular carcinoma. CHB, chronic hepatitis; PSM, propensity score matching.

Table 2. Risk of HCC in patients with compensated CHB cirrhosis receiving ETV+FZHY or ETV alone according to the cumulative use of FZHY

	Total, n=910/462	HCC, n=115/31	Hazard Ratio (95% CI)			
			Crude#	*p* value	Adjust*	*p* value
ETV group	452/231	91/20	Reference			
FZHY group	458/231	24/11				
6–12 months	82/43	5/2	0.764 (0.309, 1.889)	0.56	1.488 (0.345, 6.418)	0.594
12–36 months	242/122	10/5	0.194 (0.1, 0.375)	<0.01	0.346 (0.117, 1.027)	0.056
>36 months	134/66	9/4	0.216 (0.108, 0.432)	<0.01	0.305 (0.113, 0.823)	0.019

#Crude HR represents relative hazard ratio; *Adjusted HR represents multivariate-adjusted hazard ratio for age, white blood cell count, platelets, ALT and GGT. CHB, chronic hepatitis B; CI, confidence interval; HCC, hepatocellular carcinoma; ETV, entecavir; FZHY, Fuzheng Huayu tablets.

APRI decreased significantly after intervention. The decrease in the FZHY+ETV group was greater than that in the ETV group (p<0.01) (Table 4).

In our cohort, the LSM at the last follow-up was significantly lower in the ETV+FZHY group than in the ETV group (median 8.15 vs 11.8, p=0.003) (Supplementary Table 2), suggesting that the chemopreventive effect of FZHY on HCC is related to its antifibrotic properties.

Discussion

In this study, we found that FZHY was effective in preventing HCC occurrence in patients with HBV-related cirrhosis. We also observed that FZHY demonstrated a potential mitigating effect on portal hypertension related events. Confounding factors such as age, diabetes, and liver function may have influenced the occurrence of HCC within the initial cohort. Even among patients with known risk factors, those who received

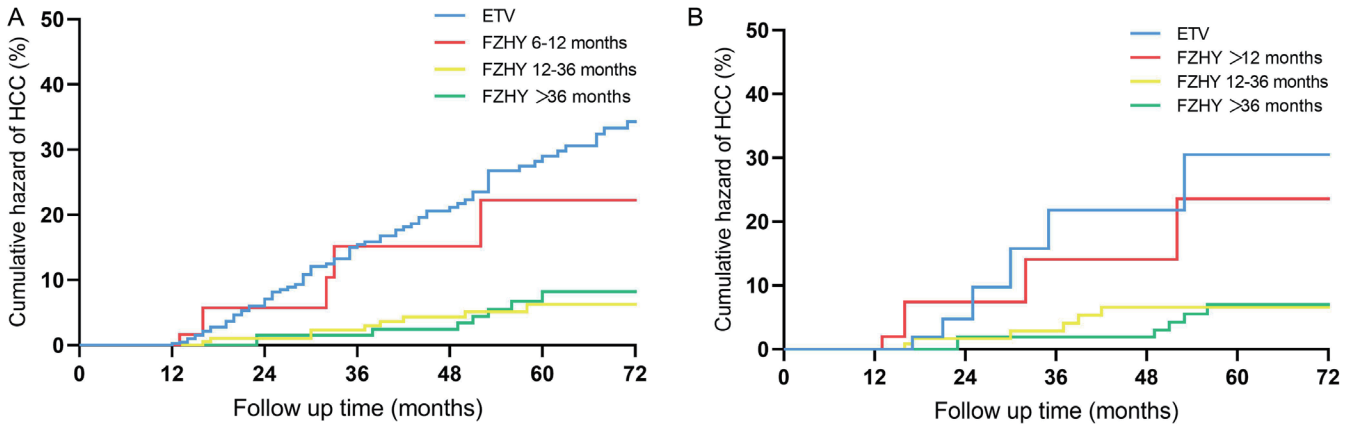

Fig. 3. The cumulative hazard of HCC and duration of FZHY treatment in patients with compensated CHB cirrhosis before (A) and after (B) PSM. ETV, entecavir; FZHY, Fuzheng Huayu tablets; HCC, hepatocellular carcinoma. CHB, chronic hepatitis B; PSM, propensity score matching.

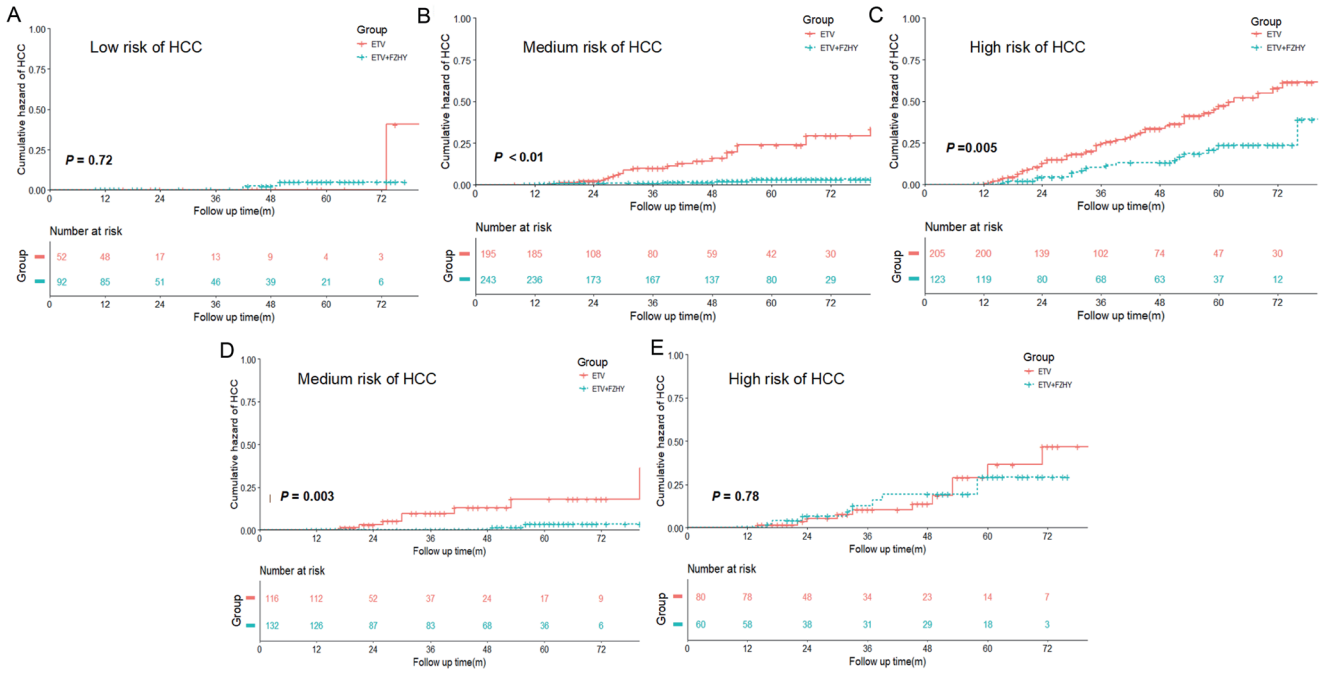

Fig. 4. Cumulative hazard of HCC based on mPAGE-B scores before (A-C) and after (D, E) PSM. ETV, entecavir; FZHY, FuzhengHuayu tablets; HCC, hepatocellular carcinoma; PSM, propensity score matching.

FZHY therapy still achieved optimal therapeutic effects. During the follow-up, patients who received FZHY in combination with ETV demonstrated a notable reduction in noninvasive indicators of liver fibrosis. These findings collectively highlight the efficacy and safety of long-term FZHY application in HCC chemoprevention.

Even though antiviral drugs can reduce the occurrence of HCC, the annual incidence of HCC in patients treated with antivirals is still 1.5–2.5%.[3] In addition to virological factors, liver fibrosis is a major factor in the development of HCC; thus, reversing fibrosis or cirrhosis is an effective strategy to prevent HCC. However, there is a lack of FDA approved antifibrosis drugs or other chemoprevention therapies. Therefore, many patients use TCM, which has a long history of treating liver disease (including cirrhosis) and several herbal products have been approved for their antifibrotic efficacy in the liver.

Liver fibrosis or cirrhosis increases the risk of developing HCC in patients with hepatitis B. Our analysis of indexes of fibrosis during follow-up between the two groups revealed that FIB-4 and APRI decreased significantly with the combined ETV and FZHY treatment compared to ETV alone ($p<0.01$) (Table 4). Previous studies have also revealed a relationship between changes in LSM during follow-up and fibrosis regression.[17,18] In our cohort, the LSM at the last follow-up in the ETV+FZHY group was significantly lower than that in the ETV group (median 8.15 vs 11.8, $p=0.003$) (Supplementary Table 2). This suggests that the chemoprevention property of FZHY against HCC may be due to its antifibrosis properties.

In the present study, the 5-year cumulative hazard of HCC in patients receiving ETV alone was 20.1% before PSM. This

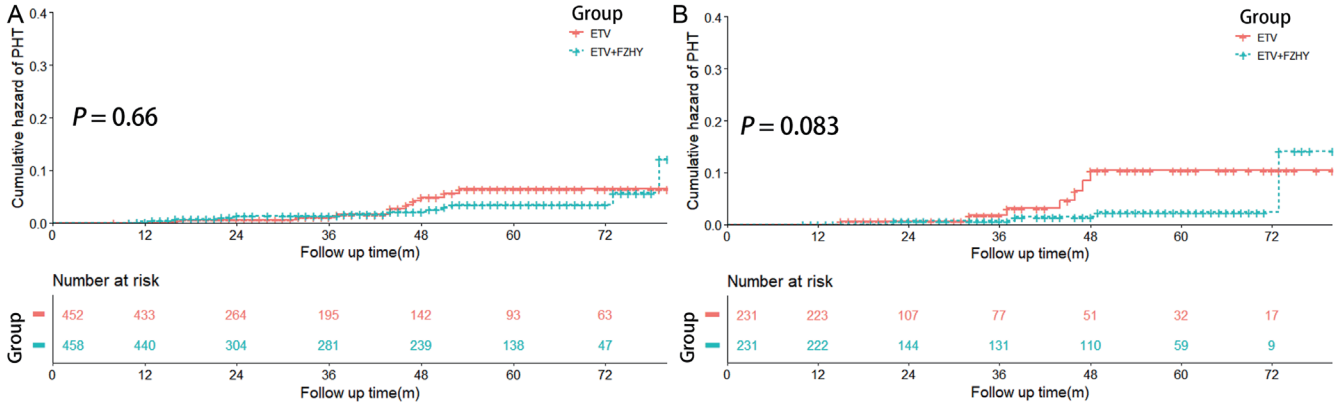

Fig. 5. The cumulative hazard of hepatic events between two groups of patients with compensated CHB cirrhosis receiving ETV+FZHY or ETV alone before (A) and after (B) PSM. The cumulative hazard of PHT-related events was lower in the ETV+FZHY group before and after PSM (Log rank $p=0.66$ and 0.083). ETV, entecavir; FZHY, Fuzheng Huayu tablets; HCC, hepatocellular carcinoma; CHB, chronic hepatitis B; PHT, portal hypertension; PSM, propensity score matching.

Table 3. Univariate and multivariate Cox proportional hazard regression analysis of prognostic factors in patients with compensated CHB cirrhosis before PSM

Factors	No. patients	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*p* values	HR (95% CI)	*p* values
Sex (Female/ Male)	230/680	0.826 (0.539, 1.267)	0.382		
Age (<45/≥45) years	380/530	0.198 (0.109, 0.361)	<0.01	0.248 (0.121, 0.509)	<0.01
Diabetes (No/ Yes)	851/59	0.26 (0.164, 0.412)	<0.01	0.232 (0.128, 0.418)	<0.01
Alcohol consumption (No/ Yes)	524/86	1.095 (0.64, 1.875)	0.741		
Family history of HBV (No/ Yes)	331/169	1.351 (0.876, 2.084)	0.174		
Family history of HCC (No/ Yes)	452/44	0.879 (0.44, 1.75)	0.715		
WBC ×109/l		1.003 (0.893, 1.128)	0.955		
HGB g/l		1.005 (0.995, 1.015)	0.314		
PLT (<140/≥140) ×109/l	573/278	1.42 (0.892, 2.261)	0.139		
ALT (<40/≥40) IU/l	621/213	1.849 (1.085, 3.151)	0.024	3.104 (1.451, 6.638)	<0.01
AST (<2ULN/≥2ULN) IU/l*	719/116	1.058 (0.591, 1.893)	0.849		
GGT (<64/≥64) IU/l	573/294	0.682 (0.455, 1.022)	0.064	0.594 (0.382, 0.923)	0.021
Alb (<35/≥35) g/l	124/702	1.552 (0.99, 2.439)	0.055	1.668 (1.021, 2.726)	0.041
TBil μmol/l		1.005 (1, 1.01)	0.07		
Cr μmol/l		0.997 (0.979, 1.014)	0.701		
AFP (<8.78/≥8.78) ng/ml	479/322	0.625 (0.418, 0.934)	0.022		
HBeAg (Negative/Positive)	470/348	0.677 (0.459, 0.999)	0.05	0.619 (0.39, 0.982)	0.041
HBV DNA (<2,000/≥2,000) IU/ml	183/628	0.633 (0.366, 1.093)	0.101		
LSM (<12.4/≥12.4) kPa	117/264	0.441 (0.144, 0.956)	0.053		
APRI		1.056 (0.992, 1.1)	0.088		
FIB-4		1.085 (1.056, 1.116)	<0.01	1.11 (1.026, 1.202)	<0.01

*The UNL of AST was 40 IU/l. APRI, AST/PLT ratio index; AFP, alpha-fetoprotein; Alb, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; GGT, γ-glutamyl transpeptidase; HGB, hemoglobin; PLT, platelet; PSM, propensity score matching; TBil, total bilirubin; WBC, white blood count; CHB, chronic hepatitis B; CI, confidence interval; LSM, liver stiffness measurement; HBV, hepatitis B virus; FIB-4, Fibrosis 4 score; HR, hazard ratio.

finding aligns with a previous study involving a Chinese cohort,[10,19] but is slightly higher than the hazard reported in other studies.[14,20] Compared to the study by Shi et al, we targeted a population of patients with compensated HCC who were receiving ETV treatment. This implies greater uniformity among the patients included in the cohort.

We also found that two noninvasive fibrosis indexes, FIB-4 and APRI, significantly decreased in both groups during follow-up. However, the ETV+FZHY group exhibited a larger decrease than the ETV group. Additionally, there was a significant difference in the LSM value after treatment between the two groups. It is important to note that the changes in LSM were not different between the two groups, given that only a limited number of eligible patients underwent measurements twice (146 cases, accounting for 1/6 of all patients), and there were noticeable variations in LSM values among different centers.

FZHY consists of a number of TCM ingredients, such as Danshen, Chongcao, Taoren, Jiaogulan, Songhuafen, and Wuweizi. The mechanisms of action underlying FZHY's antifibrosis effects in the liver likely involve multiple aspects, including the inhibition of hepatic stellate cell activation, hepatocyte protection from injury, improvement in the dedifferentiation of hepatic sinusoidal endothelial cells, and suppression of macrophage polarization.[21,22] Notably, cirrhotic livers often exhibit endothelial dysfunction and irregular vascularization, both of which can be corrected by FZHY treatment.[23] Among the various mechanisms of Chinese herbal medicine that can reduce HCC, improvement of fibrosis is a primary outcome for reducing HCC pathogenesis.

With regard to confounding factors, the existing literature indicates that age and modifiable factors such as alcohol consumption, smoking, and metabolic syndrome are risk factors for HCC in patients with CHB.[24,25] The possible mechanisms underlying this relationship may involve hepatocyte proliferation triggered by hyperinsulinemia, activation of inflammatory responses, or aldehyde dehydrogenase 2 deficiencies in cirrhotic patients.[26–28]

Our study has several limitations that should be noted. First, this was a retrospective study with unmatched baseline data, but we performed PSM to address this issue. Secondly, our study focused specifically on a population of patients with compensated CHB cirrhosis who were receiving ETV. It is important to note that patients treated with ETV may experience regression of fibrosis but remain at risk for HCC. Therefore, the beneficial effects of Fuzheng Huayu tablets for populations that have previously received antiviral treatments require further investigation.

Conclusions

This retrospective cohort study suggests that combining ETV

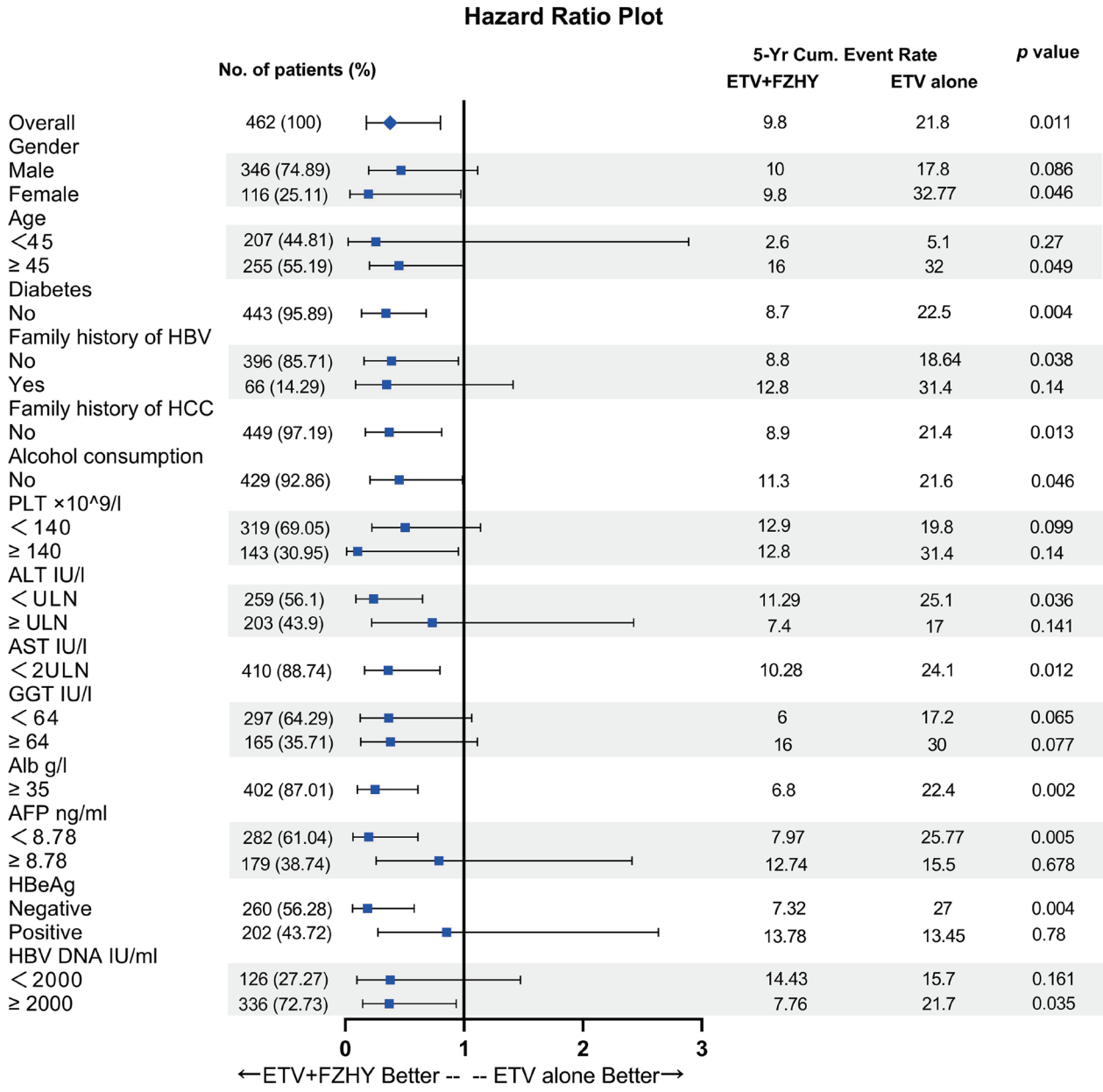

Fig. 6. Subgroup analysis based on Cox regression after PSM for HCC hazard between two groups of patients with compensated CHB cirrhosis receiving ETV+FZHY or ETV alone. ULN of ALT, 45 IU/l for men and 30 IU/l for women; ULN of AST, 40 IU/l. ETV, entecavir; FZHY, FuzhengHuayu tablets; HBV, hepatitis B virus; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; AFP, alpha-fetoprotein; Alb, albumin; PSM, propensity score matching; HCC, hepatocellular carcinoma.

with FZHY can potentially reduce the cumulative incidence of HCC in patients with compensated CHB cirrhosis. This benefit may be attributed to the antifibrotic property of FZHY. These findings provide a promising clinical approach for HCC chemoprevention. Further studies including large-scale, prospective, and randomized clinical trials are required to further validate our findings.

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Conflict of interest

CL has been an Editorial Board Member of *Journal of Clinical and Translational Hepatology* since 2018. The other authors

Table 4. Noninvasive indicators during follow-up between the two groups of patients with compensated CHB cirrhosis receiving ETV+FZHY or ETV alone

Non-invasive indicators	Group	n	Time				Group		Time*Group	
			Baseline	1-yr treatment	Last Follow-up	F	*p* values	F	*p* values	
APRI	ETV	277	1.786±2.443	0.954±0.774	0.892±1.424	53.430	<0.01	27.007	<0.01	4.464	0.025
	ETV+FZHY	293	1.103±1.772	0.678±0.508	0.577±0.542						
FIB-4	ETV	277	4.914±4.691	3.744±3.122	3.603±3.741	50.833	<0.01	34.529	<0.01	4.193	0.024
	ETV+FZHY	293	3.109±3.367	2.564±2.189	2.272±2.124						

APRI, AST/PLT ratio index; CHB, chronic hepatitis B; FIB-4, Fibrosis 4 score; ETV, entecaivr; FZHY, Fuzheng Huayu tablets.

have no conflict of interests related to this publication.

Author contributions

Project conception and organization (CL, ZZ, QX); clinical examinations and follow-up evaluations (YH, XLi, KS, HX, JH, MX, CZ, KZ, YZ, HW, XLiu, WZ, YM, XS); statistical analysis (HF); figures and tables (HF); literature and interpretation (HF, ZZ, CL); and manuscript preparation (HF, ZZ, SL, CL).

Ethical statement

All study procedures were conducted in accordance with the Helsinki Declaration of 1975 and were approved by the Medical Ethics Committee of Shuguang Hospital (2018-558-17-01). Written informed consent was waived.

Data sharing statement

The data used in support of the findings of this study are included within the article.

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