




Original Article

Efficacy and Safety of Yanggan Jian in Hepatitis B Virus-related Decompensated Cirrhosis: A Randomized, Double-blind, Controlled Trial

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Abstract

Background and Aims: The aim was to evaluate the efficacy and safety of Yanggan Jian (YGJ) in HBV-infected patients with decompensated cirrhosis. **Methods:** This randomized, double-blind controlled trial enrolled 160 patients with HBV-related decompensated cirrhosis who were already receiving or about to start antiviral therapy. Patients were randomly assigned to receive YGJ or placebo for 24 weeks, and were followed-up to 36 weeks. The primary outcome was the proportion of patients with a ≥ 2 point reduction in Child-Turcotte-Pugh (CTP) score from baseline at week 24. Secondary outcomes were CTP class and score, serum liver function indices, mortality, incidence of hepatocellular carcinoma and variceal bleeding. **Results:** The proportion of patients with a CTP score reduction ≥ 2 was significantly greater in the YGJ than in the placebo group ($p=0.009$); the percentage of patients with CTP class C was significantly less than that in the placebo group ($p<0.05$), and the YGJ group had a significantly greater mean change from baseline in CTP score at week 24 ($p=0.034$). The improvement in measured values and change from baseline of prothrombin time, serum albumin, platelets, cholinesterase, international normalized ratio, and activated partial thromboplastin time were significantly better with YGJ than with placebo. Between-group differences in cumulative rates of variceal bleeding, hepatocellular carcinoma, death,

or the frequency of any adverse event (AE), AEs related to treatment, or discontinuation because of AEs were not significant. **Conclusions:** YGJ significantly improved CTP scores and hepatic synthetic and reserve function in patients with HBV-related decompensated cirrhosis, and was safe and well tolerated.

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Introduction

Cirrhosis is the end-stage of various chronic liver diseases and a leading cause of morbidity and mortality worldwide. In 2017, approximately 1.32 million deaths were attributable to liver cirrhosis worldwide, accounting for 2.4% of total deaths in that year.¹ Most patients with cirrhosis die of hepatic decompensation. In China, hepatitis B virus (HBV) infection is the most common cause of cirrhosis. Although oral antiviral drugs are effective in improving hepatic function and survival outcomes of patients with viral hepatitis-related decompensated cirrhosis,² the median survival time decreases from 12 to 2–4 years once compensated cirrhosis progresses to the stage of decompensation³ and imposing a heavy healthcare cost burden.⁴ Liver transplantation is the only effective treatment for patients with decompensated cirrhosis, a donor shortage and high medical costs are significant barriers to its wider use. There is a growing need for therapies to improve the quality of life and survival of patients with decompensated cirrhosis, and reduce the mortality and healthcare costs.

Traditional Chinese medicine (TCM) is a commonly used complementary and alternative therapy for patients with chronic liver diseases in China. It has been shown to improve clinical symptoms and the effectiveness of antiviral drugs for

Keywords: Decompensated cirrhosis; Yanggan Jian; Traditional Chinese medicine; Clinical trial; Child-Turcotte-Pugh.

Abbreviations: γ -GT, gamma glutamyl transpeptidase; AE, adverse event; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CHE, cholinesterase; CTP, Child-Turcotte-Pugh; DBil, direct bilirubin; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; INR, international normalized ratio; PA, prealbumin; TBil, total bilirubin; TBA, total bile acids; TCM, traditional Chinese medicine; YGJ, Yanggan Jian.

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HBeAg clearance in patients with HBV infection,⁵ reduce the risk of cirrhosis⁶ and hepatocellular carcinoma (HCC),⁷ and increase the 5-year survival of patients with decompensated cirrhosis.⁸ Clinical and experimental studies have demonstrated the effectiveness of Yanggan Jian (YGJ), a Chinese herbal compound, for the prevention and treatment of cirrhosis,^{9–11} but there is a lack of evidence from randomized clinical trials. In this study, we evaluated the short-term efficacy and safety of YGJ in HBV-infected patients with decompensated cirrhosis. Its efficacy and safety were assessed by Child-Turcotte-Pugh (CTP) score, hepatic function, incidence of HCC, variceal bleeding, and mortality.

Methods

Study design

This was a multicenter, randomized, double-blind, placebo-controlled clinical trial conducted at five medical centers in China, Shuguang Hospital affiliated to Shanghai University of Traditional Chinese Medicine, Putuo Hospital, Shanghai University of Traditional Chinese Medicine, Xiamen Hospital of Traditional Chinese Medicine, Linyi People's Hospital, and Huai'an No. 4 People's Hospital. Written informed consent was obtained from trial participants or their legal representatives. The study was conducted following the ethical guidelines of the 1975 Declaration of Helsinki and the regulations on quality management of clinical trials in China. The study protocol and the informed consent process were reviewed and approved by the Institutional Review Board of Shuguang Hospital affiliated to Shanghai University of Traditional Chinese Medicine (2015-0386-14-02).

Patients

Inclusion criteria: Patients 18–72 years of age with a history of HBV infection, positive for hepatitis B surface antigen (HBsAg) or HBV-DNA and already receiving or were about to start antiviral therapy were eligible if they had hepatic decompensation, i.e. a CTP score ≥ 7 and deficiency of liver and kidney Yin Syndrome. The diagnosis of TCM Syndromes of patients at the baseline evaluation was performed by two experienced TCM physicians. The main symptoms were lower back pain or weakness of the waist and knee; rib, dull ache aggravated by fatigue; dry eyes; and red tongue with little or no moss.

Exclusion criteria: Patients with hepatitis C virus coinfection, hepatitis D virus, or other chronic severe hepatitis, acute or subacute liver failure, pregnant or lactating women, a history of a serious primary disease including malignant tumors, human immunodeficiency virus infection, severe kidney dysfunction, severe chronic obstructive pulmonary disease, or chronic congestive heart failure were excluded.

Interventions: In addition to antiviral drugs and standard medical therapy with nutritional supplements, diuretics, beta blockers, and other supportive symptomatic treatment, the two study groups were treated with either YGJ or placebo three times a day for 24 weeks. YGJ is a TCM herbal formulation of including Radix Rehmanniae (Shengdihuang), Radix Glehniae (Beishashen), Radix Angelicae Sinensis (Danggui), Lycii Fructus (Gouqizi), Radix Ophiopogonis (Maidong), and Toosendan Fructus (Chuanlianzi). The final product was supplied as bags containing 6.6 g of concentrated granules produced in a series of extractions during manufacturing. The placebo was supplied as bags containing 6.6 g of excipient with 5% YGJ. Both YGJ and the placebo were produced by Jiangyin Tianjiang Pharmaceutical Co. Ltd., China. The chemical profiles

of YGJ and placebo are shown in Supplementary File 1 and Supplementary Figure 1.

Measurements: Both study groups were followed-up for 36 weeks with regular outpatient department visits. Abdominal ultrasonography, liver function tests, serum hepatitis viral markers including HBsAg, hepatitis B surface antibody (anti-HBs), hepatitis B e antigen (HBeAg), hepatitis B e antibody (anti-HBe) and hepatitis C antibody (anti-HBc), routine blood, renal function, and coagulation function tests, and HBV-DNA assays were performed at baseline, 12, 24, and 36 weeks. Change in CTP score and development of new complications including ascites, hepatic encephalopathy, esophageal and gastric variceal bleeding, HCC, and death, were monitored.

Sample size: The sample size was estimated by referring to a previous report of 32% of patients with a ≥ 2 point reduction in CTP score after treatment with entecavir.¹² We factored a 25% increase in the proportion of patients showing ≥ 2 point reduction in CTP score after treatment with YGJ in combination with antiviral drugs compared to that with ETV alone (i.e. to 57%). For a two-sided α of 0.05 and 80% statistical power, the calculated size of each group was 60, for a total of 120 study subjects. Factoring an attrition rate of 25%, the estimated total sample size was 160.

Randomization and blinding: A total of 160 patients were randomly assigned in equal numbers to the YGJ or placebo group. Random codes were generated by block randomization using SAS 9.4 software. The selected block length and random initial seed parameters were sealed in opaque envelopes that were under the control of personnel who were not involved in data management, study procedures, or the statistical analysis. The appearance and taste of the placebo, which consisted of excipient and 5% YGJ, were similar with those of YGJ to ensure successful double-blinding of the group identity. Group identity was revealed at the end of follow-up.

Outcome assessment: The primary outcome was the proportion of patients with a ≥ 2 point reduction in CTP score at week 24 compared with baseline. Secondary outcomes included CTP class and score; serum liver function indices including aspartate aminotransferase (AST), alanine transaminase (ALT), gamma glutamyl transpeptidase (γ -GT,) alkaline phosphatase (ALP), cholinesterase (CHE), prealbumin (PA), albumin (ALB), total bilirubin (TBil), direct bilirubin (DBil), and total bile acids (TBA); mortality; incidence of HCC and variceal bleeding. Safety-related endpoints included the frequencies and characteristics of adverse events (AEs), serious AEs, drug discontinuation, and possible relatedness to the study drug as assessed by the investigator. AEs were monitored throughout the study.

Statistical analysis

Statistical analysis was performed by study investigators at the Clinical Research Center, Shanghai University of Traditional Chinese Medicine in a blinded manner using SAS 9.4 software (Cary, NC, USA). A full analysis set (FAS) of all patients who were randomized to at least one dose of the study drug and had at least one post-treatment evaluation of clinical effectiveness and an intention-to-treat (ITT) set were evaluated. Continuous variables were reported as means \pm standard deviation or medians and interquartile range, as appropriate. Between-group differences were assessed by analysis of variance or *t*-tests. Categorical variables were reported as frequency and percentage (%) and compared with chi-squared or Fisher's exact tests. *p*-values of < 0.05 were considered of statistically significant.

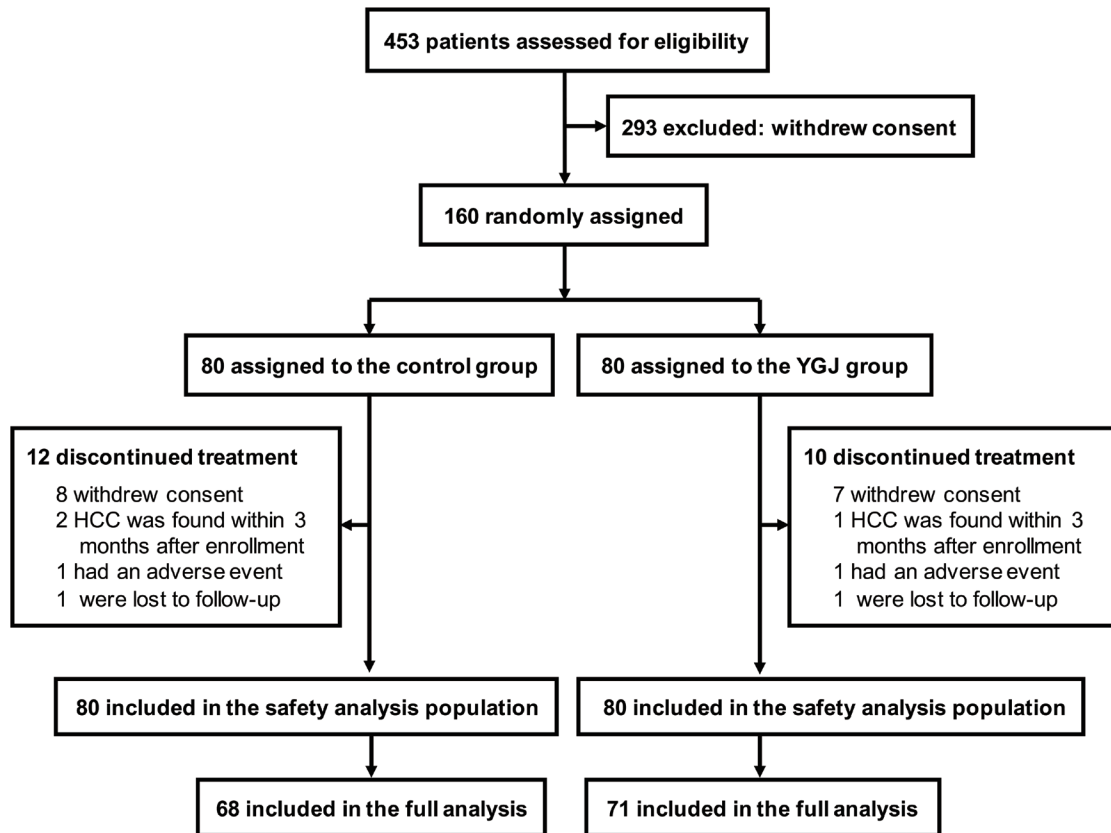


Fig. 1. Flow diagram of the study design.

Results

Subject disposition

Patients were recruited from May 2015 to March, 2020. A total of 453 were screened, 293 of whom were excluded because of lack of intention to participate, and the remaining 160 patients with HBV-infected cirrhosis were enrolled. The subject disposition is shown in Figure 1. At the 36-week follow-up, 22 of the 160 patients had discontinued treatment, three had developed liver cancer within 3 months after enrollment, two discontinued because of AEs, 15 withdrew consent, two were lost to follow-up, and 21 were excluded from the FAS. The average age was 53.7 ± 9.6 years (IQR 26.0–72.0 years), 69.8% were men, the average body mass index was 23.0 ± 3.5 kg/m², and the average CTP score was 8.5 ± 1.7 . The baseline characteristics of the two groups were balanced (Table 1, Supplementary Tables 1–3). The globulin concentration was higher in the placebo than in the YGJ group ($p=0.009$), and the red blood cell count was lower ($p=0.032$, Supplementary Tables 2 and 3). The placebo group had a higher proportion of patients receiving concomitant treatment with other herbal decoctions ($p=0.002$) and Chinese patent drugs ($p=0.012$; Table 1, Supplementary Table 1).

Changes in CTP score

The CTP scores of both groups were improved at week 24, but the proportion of patients in the YGJ group with an improvement of ≥ 2 points was significantly greater in

the YGJ than in the placebo group [FAS, 62.0% (95% CI: 53.5–70.0) vs. 39.7% (95% CI: 31.4–48.4), $p=0.009$; ITT, 55.0% (95% CI: 46.9–62.9) vs. 33.8% (95% CI: 26.5–41.6), $p=0.007$; Table 2, Supplementary Table 4). The baseline CTP class distribution did not differ between the two groups, but was significantly different at week 24 ($p=0.017$). At week 24, the percentage of CTP class C patients in the YGJ group was significantly less than that in the placebo group ($p<0.05$; Table 2), which suggests that YGJ improved the CTP class. The baseline CTP scores in the YGJ and placebo groups were not significantly different (8.4 ± 1.7 vs. 8.7 ± 1.7 , $p=0.248$; Table 1), and the CTP scores in YGJ group were significantly lower than those in the placebo group at week 12 (8.0 ± 2.17 vs. 7.2 ± 1.75 , $p=0.018$; week 24 (6.50 ± 1.60 vs. 7.50 ± 2.38 , $p=0.005$); and week 36 (6.6 ± 1.74 vs. 7.4 ± 2.49 , $p=0.033$; Fig. 2). At week 24, the mean change in CTP score from baseline in the YGJ group [-1.8 (95% CI: -2.2 to 1.4)] was significantly greater than that in the placebo group [-1.2 (95% CI: -1.7 to -0.7 , $p=0.034$; Table 2). There was no significant between-group difference in the proportion of patients with mild or moderate to severe ascites at baseline; but, at 24 weeks, the proportion of patients with mild or moderate to severe ascites in the YGJ group was significantly lower than that in the placebo group ($p=0.024$; Supplementary Table 5).

Change in hepatic function

Through week 24, hepatic function improved from baseline in both groups, as indicated by ALB, prothrombin time

Table 1. Baseline demographics and disease characteristics (full analysis set)

Variable	Placebo group (n=68)	YGJ group (n=71)	p-value
Age, years	54.2±9.41	52.7±9.61	0.349
Male	43 (63.2)	54 (76.1)	0.100
BMI (kg/m ²)	22.7±2.9	23.2±4.0	0.378
History of hepatitis B (months)	80.0 (13.0, 196.0)	96.0 (12.0, 221.0)	0.916
History of liver cirrhosis (months)	8.0 (1.0, 41.0)	23.5 (2.0, 91.0)	0.080
Antiviral drugs			
ETV	48 (70.6)	46 (64.8)	0.764
TDF	13 (19.1)	16 (22.5)	
Other	7 (10.3)	9 (12.7)	
First treatment with antiviral drugs	28 (42.4)	22 (32.4)	0.228
HBeAg positivity	22 (32.4)	25 (35.2)	0.722
HBV-DNA (log ₁₀ IU/mL)	1.8±2.4	1.7±2.4	0.929
HBV-DNA (positive)	22 (32.4)	24 (33.8)	0.856
herbal decoction pieces	29 (45.3)	13 (19.7)	0.002
Chinese patent drug	44 (68.8)	31 (47.0)	0.012
Diabetes mellitus	13 (20.3)	19 (29.2)	0.241
Hypertension	9 (23.7)	8 (22.9)	0.933
Esophageal varices	33 (60.0)	38 (66.7)	0.464
Previous variceal bleeding	14 (25.5)	20 (35.1)	0.268
CTP score	8.7±1.7	8.4±1.7	0.248
CTP class			
A	3 (4.4)*	5 (7.0)*	0.563
B	46 (67.6)	48 (67.6)	
C	19 (27.9)	18 (25.4)	
PT (s)	17.34±2.972	16.86±2.832	0.332
Bilirubin (μmol/L)	50.150±29.599	49.578±41.791	0.928
Albumin (g/L)	30.215±5.303	31.147±6.481	0.356
Creatinine (μmol/L)	69.881±23.289	71.572±24.594	0.687
Ascites			
None	23 (33.8)	25 (35.2)	0.993
Mild	24 (35.3)	23 (32.4)	
Moderate to severe	21 (30.9)	23 (32.4)	
Hepatic encephalopathy			
None	64 (94.1)	68 (95.8)	0.736
Stage 1–2	3 (4.4)	2 (2.8)	
Stage 3–4	1 (1.5)	1 (1.4)	

Data are n (%) or mean±SD. *CTP score at time of eligibility determination was ≥7. BMI, body mass index, CTP, Child-Turcotte-Pugh; ETV, entecavir PT, prothrombin time; TDF, tenofovir disoproxil fumarate.

(PT), and platelet count (Table 3). The improvement in the YGJ group was significantly greater than that in the placebo group (ALB 6.175±7.144 vs. 3.248±6.307 g/dL, $p=0.016$; PT $-1.62±2.091$ vs. $-0.37±2.461$ s, $p=0.005$; platelets $-4.8±21.9$ vs. $9.4±26.5 \times 10^9$, $p=0.003$; Table 3), and pre-albumin was significantly higher than in the placebo group ($130.9±51.7$ vs. $105.8±52.2$, and 95% CI: 116.7–145.2

vs. 91.9–119.7, $p=0.013$; Supplementary Table 6).

Biochemical response

At week 24, the AST and DBil levels in the YGJ group were significantly lower than those in the placebo group (AST

Table 2. CTP score change at week 24 (full analysis set)

Variable	Placebo group (n=68)	YGJ group (n=71)	p-value
CTP score ≥ 2 point reduction, n (%)	27 (39.7)	44 (62.0)	0.009
95% CI	31.4, 48.4	53.5, 70.0	
CTP class, n (%)			
A	29 (42.6)	40 (56.3)	0.017
B	22 (32.4)	23 (32.4)	
C	13 (19.1)	2 (2.8) *	
Unknown	4 (5.9)	6 (8.5)	
CTP score change from baseline			
n	64	65	
Mean \pm SD	-1.2 \pm 2.01	-1.8 \pm 1.67	0.034
Median	-1.0	-2.0	
95% CI	-1.7, -0.7	-2.2, -1.4	

* $p < 0.05$, the percentage of patients with CTP class C in the YGJ group was significantly less than that in the placebo group. CTP, Child-Turcotte-Pugh; CI, confidence interval.

38.0 \pm 15.1 vs. 44.7 \pm 18.9, $p=0.033$ and DBil 9.8 \pm 6.7 vs. 14.4 \pm 14.1, $p=0.023$; Supplementary Table 6). In addition, both the cholinesterase concentration (4.9 \pm 1.7 vs. 3.9 \pm 1.7, $p < 0.001$) and the change in concentration from baseline (1.5 \pm 1.6 vs. 0.8 \pm 1.5, $p=0.009$) in the YGJ group were significantly greater than those in the placebo group (Supplementary Table 6).

Change in coagulation function

At week 24, the degree of improvement in both the value of the international normalized ratio (INR, 1.2 \pm 0.2 vs. 1.4 \pm 0.4, $p=0.002$) and activated partial thromboplastin time (APTT, 39.2 \pm 4.6 vs. 41.8 \pm 6.4, $p=0.019$) and the change from baseline in the INR (-0.1 \pm 0.2 vs. -0.0 \pm 0.3, $p=0.021$) and APTT (-3.2 \pm 5.4 vs. -0.6 \pm 5.7, $p=0.026$) in the YGJ group were significantly better than those in the placebo group (Table 4).

Incidence of variceal bleeding and HCC and survival outcome

At week 36, there were no significant between-group difference in the cumulative rates of variceal bleeding, HCC and death (Table 5, Supplementary Table 7). Ten of these sub-

jects died due to liver failure ($n=8$), massive bleeding from ruptured esophageal and gastric varices ($n=1$), or unknown cause ($n=1$) (Supplementary Table 8). At week 24, mortality was 4.4% in the placebo group and 1.4 in the YGJ group (FAS $p=0.581$; Table 5).

Safety

AEs were generally transient and mild-to-moderate in severity. AEs associated with treatment included diarrhea and increased stool frequency. One patient in each group discontinued the study treatment because of AEs. There were no significant between-group differences in the frequency of any AEs, treatment-associated AEs, or discontinuation because of AEs (Table 6, Supplementary Table 9). In addition, no renal function abnormalities (e.g., BUN, Cr, or UA) were observed at week 24 and 36 (Supplementary Table 10).

Discussion

Liver transplantation is the only effective treatment for patients with decompensated cirrhosis. Unfortunately, many patients die while on the waiting list for transplantation because of a shortage of live donors. Treatment of HBV-infected decompensated cirrhosis is mainly etiological and symptomatic. Antiviral therapy promotes HBV DNA clearance in the vast majority of patients (Supplementary Table 11), improves liver function and retards disease progression to some extent, but the effectiveness of antiviral drugs is less than 40%, and more than 60% of patients fail to recover liver function.^{13,14} Our finding that only 39.7% of patients in the placebo group had a reduction in CTP score of ≥ 2 points with antiviral therapy, is consistent with other studies that reported reductions in 32%¹² and 36%¹⁴ of patients. YGJ significantly improved hepatic function, reserve, and quality of life (e.g. low back pain, weakness of the waist and knees, and so on). YGJ was safe and well tolerated.

YGJ has been shown to be an effective treatment for liver cirrhosis in animal models.^{15,16} It is widely used for patients with liver cirrhosis in clinical settings; but there is a lack of evidence of its efficacy and safety. In this randomized, double-blind, placebo-controlled trial, 62% of patients in the YGJ group achieved ≥ 2 point reduction in CTP score, which

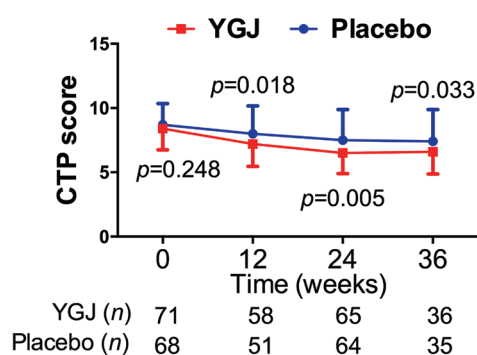


Fig. 2. Child-Turcotte-Pugh score at weeks 0, 12, 24, and 36.

Table 3. Measured values and change from baseline in hepatic synthetic function at week 24

Variable		Placebo group	YGJ group	p-value
Measured value				
PT (s)	<i>n</i>	64	65	
	Mean±SD	16.99±3.712	15.13±1.789	0.001
	Median (range)	15.90 (12.2, 29)	14.75 (11.8, 20.4)	
	95% CI	16.01–17.98	14.64–15.62	
Platelets (10 ⁹ /L)	<i>n</i>	56	54	
	Mean±SD	82.6±49.22	84.8±49.37	0.815
	Median (range)	72.0 (10–313)	77.5 (18–202)	
	95% CI	69.4–95.8	71.3–98.3	
Albumin (g/L)	<i>n</i>	64	65	
	Mean±SD	33.3±7.2	37.2±6.0	0.001
	Median (range)	33.0 (16–48)	37.5 (23–49)	
	95% CI	31.5–35.1	35.7–38.7	
Change from baseline				
PT (s)	<i>n</i>	64	65	
	Mean±SD	−0.37±2.461	−1.62±2.091	0.005
	Median (range)	−0.60 (−4.7, 8.3)	−1.15 (−7.3, 1.9)	
	95% CI	−1.02, 0.28	−2.19, −1.05	
Platelets (10 ⁹ /L)	<i>n</i>	56	54	
	Mean±SD	−4.8±21.92	9.4±26.50	0.003
	Median (range)	−4.5 (−56, −41)	3.5 (−38, −98)	
	95% CI	−10.7–1.2	2.2–16.7	
Albumin (g/L)	<i>n</i>	64	65	
	Mean±SD	3.248±6.307	6.175±7.144	0.016
	Median (range)	2.960 (−16, 16.8)	5.270 (−9, 28)	
	95% CI	1.646–4.850	4.390–7.959	

CI, confidence interval; PT, prothrombin time.

was significantly better than that in the placebo group. YGJ also improved CTP status, CTP class distribution, and the percentage of patients with CTP class C, measured values, and change from baseline in CTP scores. Improvement in CTP score and class in the YGJ group was primarily driven by increase in albumin levels, decrease in PT, and improvement in ascites.

The physiological functions of ALB include maintenance of plasma osmotic pressure, anti-oxidative and antithrombotic activity, and immunoregulation.^{17,18} Evidence from clinical trials shows that long-term ALB administration to patients with cirrhosis increases the serum ALB level, reduces the occurrence of bacterial infections and renal failure, improves circulatory dysfunction, controls ascites, and improves survival.^{19,20} In this study, YGJ significantly increased the ALB level and improved ascites in patients with decompensated cirrhosis, which is consistent with results obtained in animal models of liver fibrosis, where YGJ significantly increased the serum and liver ALB levels.^{10,16} ALB is exclusively synthesized by hepatocytes; therefore, YGJ likely increased ALB level because it protected against hepatocyte damage and apoptosis and promoted the proliferation of hepatocytes.^{16,21} In addition, although the liver has remarkable regenerative capacity after acute damage or hepatectomy, the regenera-

tive ability is severely impaired in decompensated cirrhosis. YGJ has been shown to promote the differentiation of bone marrow mesenchymal stem cells into hepatocyte-like cells to reverse dimethyl nitrosamine-induced liver cirrhosis.²² In our previous study, YGJ was found to promote the differentiation of fetal liver stem/progenitor cells into hepatocytes after transplantation to repair liver cirrhosis.¹⁰ The results suggest that YGJ promoted liver regeneration. In this trial, improvement in liver function including CTP, serum ALB, PT, and ascites control likely reflect the effects of YGJ in promoting liver regeneration.

Mortality was 1.4% (*n*=1) in the YGJ group, which was less than that in the placebo group (*n*=4, 4.4%), but the difference was not statistically significant owing to the small sample size. The CTP score is considered to be a very good predictor of the short-term mortality of patients with end-stage liver disease.^{23,24} In this study, As YGJ significantly improved CTP scores, it may be found to improve the short-term mortality of decompensated cirrhotic patients. However, another clinical trial with longer treatment duration is required to provide more robust evidence.

There were no significant between-group differences in WBC, Cr, BUN, or UA, suggesting that YGJ had no adverse effects on renal function or white blood cells during treatment

Table 4. Measured values and change from baseline in coagulation function at week 24

Variables		Placebo group	YGJ group	p-value
Measured value				
INR	<i>n</i>	64	65	
	Mean±SD	1.405±0.411	1.210±0.189	0.002
	Median (range)	1.260 (0.94–2.73)	1.155 (0.89–1.75)	
	95% CI	1.292–1.517	1.156–1.263	
APTT (s)	<i>n</i>	64	65	
	Mean±SD	41.796±6.415	39.183±4.551	0.019
	Median (range)	40.300 (27.5–60.7)	39.000 (29.1–51.3)	
	95% CI	40.010–43.582	37.890–40.476	
Change from baseline				
INR	<i>n</i>	64	65	
	Mean±SD	−0.019±0.267	−0.134±0.232	0.021
	Median (range)	−0.055	−0.080	
	95% CI	−0.092, 0.054 (−0.48, 0.92)	−0.200, −0.068 (−0.81, −0.26)	
APTT (s)	<i>n</i>	64	65	
	Mean±SD	−0.614±5.658	−3.186±5.386	0.026
	Median (range)	0.200 (−18.1, 14.9)	−3.000 (−17.6, 6.4)	
	95% CI	−2.222, 0.994	−4.804, −1.567	

APTT, activated partial thromboplastin time; CI, confidence interval; INR, international normalized ratio.

of decompensated cirrhosis. Baseline severity of liver disease is an important factor affecting study safety, especially early mortality and the incidence of AEs. Patients with more severe liver disease were enrolled in this trial. The baseline CTP score was 8.5. Serious AEs that may be expected in patients with decompensated cirrhosis include lactic acidosis and renal failure, but none of those events occurred in this study. There were also no significant between-group dif-

ferences in the frequency of any AEs, AEs related to treatment, or study discontinuation because of AEs. The most frequent AEs in the YGJ group were gastrointestinal side effects, which were relieved after the patient had adapted to YGJ. In addition, for patients with decompensated cirrhosis, the increase in defecation frequency may have helped reduce the diffusion of intestinal endotoxins and ammonia metabolism. YGJ was safe and well tolerated.

Table 5. Outcomes of HCC occurrence and survival through 36 weeks (full analysis set)

	Placebo group (n=68)	YGJ group (n=71)	p-value
24 weeks			
HCC, <i>n</i> (%)	1 (1.5)	2 (2.8)	>0.999
Death, <i>n</i> (%)	3 (4.4)	1 (1.4)	0.359
Variceal bleeding, <i>n</i> (%)	1 (1.5)	2 (2.8)	>0.999
Liver transplantation, <i>n</i> (%)	1 (1.5)	1 (1.4)	>0.999
36 weeks			
HCC, <i>n</i> (%)	1 (1.5)	2 (2.8)	>0.999
Death, <i>n</i> (%)	6 (4.6)	4 (4.3)	0.526
Variceal bleeding, <i>n</i> (%)	2 (2.9)	2 (2.8)	>0.999
Liver transplantation, <i>n</i> (%)	1 (1.5)	1 (1.4)	>0.999

HCC, hepatocellular cancer.

Table 6. Summary of clinical adverse events

	Placebo group (n=80)	YGJ group (n=80)	p-value
Adverse event, <i>n</i> (%)	2 (2.5)	6 (7.5)	0.276
Discontinuation due to Adverse event, <i>n</i> (%)	1 (1.3)	1 (1.3)	>0.999

Some limitations of this study should be considered while interpreting the results. The duration of treatment and follow-up in this trial were relatively short. Second, the total dose of diuretics and other drugs, according to clinical status and requirement, taken by patients during the trial were not recorded. A larger, longer, and more rigorous multicenter randomized controlled trial is required to further confirm the safety and efficacy of YGJ.

In conclusion, the safety was acceptable, and YGJ was effectiveness in patients with HBV-related decompensated cirrhosis. YGJ significantly improved CTP scores, hepatic synthetic function and reserve, quality of life, and controlled ascites. Therefore YGJ can be considered a suitable complementary and alternative therapy for patients with HBV-infected decompensated cirrhosis.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (PL), acquisition of data (LC, CZ, WY, WL, HZ, HC, DX, CW, JC), drafting of the manuscript (JC), critical revision of the manuscript for important intellectual content (PL, JC), and administrative duties including study supervision (PL, HZ, YM).

Data sharing statement

All relevant data are available from the corresponding author upon reasonable request.

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