

Original Article

Influences of Jieyu Ruanjian Huoxue prescription on hepatic fibrosis indices and APRI in patients with hepatitis B cirrhosis

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Abstract: Objective: To investigate the influences of Jieyu Ruanjian Huoxue prescription on hepatic fibrosis indices and aspartate aminotransferase to platelet ratio index (APRI) in patients with hepatitis B cirrhosis (HBC). Methods: A total of 140 patients with hepatitis B complicated with cirrhosis who received treatment in our hospital from January 2019 to December 2019 were selected as the research subjects. and According to the difference of intervention methods, the patients were divided into the study group (n=80, conventional treatment combined with Jieyu Ruanjian Huoxue prescription) and the control group (n=60, conventional treatment). The clinical intervention effects, changes in hepatic fibrosis indices and hepatic function indices, and levels of inflammatory factors before and after intervention were analyzed. In addition, Pearson correlation analysis was conducted to analyze the correlation between fibrosis indices and hepatic function indices in patients with HBC. Results: The overall response rate in the study group was markedly higher than that in the control group (98.75% vs. 91.67%, $P < 0.05$). The levels of hyaluronic acid (HA), Type IV collagen (IV-C), aspartate aminotransferase (AST), alanine aminotransferase (ALT), APRI, interleukin-2 (IL-2) and tumor necrosis factor-alpha (TNF- α) in the study group were lower than those in the control group ($P < 0.05$) during the 1-6 months of follow-up treatment. Pearson correlation analysis exhibited that hepatic fibrosis indices (HA and IV-C) were positively correlated with liver function indices (AST and ALT) ($P < 0.05$). Conclusion: Jieyu Ruanjian Huoxue prescription can remarkably improve the hepatic fibrosis, abnormal hepatic function, and the level of inflammatory factors in patients with HBC, exhibiting a satisfactory efficacy. Therefore, Jieyu Ruanjian Huoxue prescription is worthy of clinical promotion and implementation.

Keywords: Jieyu Ruanjian Huoxue prescription, hepatitis B cirrhosis, hepatic fibrosis, APRI, influences

Introduction

Hepatitis B virus (HBV) is a common pathogen worldwide [1]. The statistics show that about 2 billion people are infected with HBV worldwide, about 400 million people carry HBV, and about 20 million patients suffer from chronic hepatitis B (CHB). The epidemiological studies suggest that there are 800,000 cases with liver function failure induced by HBV infection and liver cancer after cirrhosis every year, and HBV ranks 15th among all fatal diseases, indicating that HBV infection has become a global public health concern [2, 3]. Clinical practices show that pathogenic bacteria can cause sustained and chronic damages to the body, and multiple complications (e.g., decompensated hepatic

function, cirrhosis or hepatocellular carcinoma) may occur in patients with advanced HBV infection after the occurrence of HBV infection. Therefore, it is imperative to carry out early intervention on patients with HBV infection [4, 5].

Cirrhosis is a common clinical symptom in patients with middle and advanced hepatitis B, which can further aggravate liver function damage and induce hepatic fibrosis. The progression of hepatic fibrosis also further aggravates patients' conditions [6, 7]. In traditional Chinese medicine (TCM), there are a well-developed syndrome differentiation system and regimens for hepatitis B. According to TCM, asthenia of healthy energy and blood stasis are the patho-

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genesis of HBC, leading to liver and gallbladder stasis. Therefore, clinical treatment should be performed to activate blood circulation and dissipate blood stasis, eliminate dampness and heat, and invigorate the kidney and nourishing the liver, so as to treat both manifestation and root cause of disease [8]. Jieyu Ruanjian Huoxue prescription, a well-known TCM prescription, is composed of *Astragalus membranaceus*, *Salvia miltorrhiza*, peach kernel, radix aucklandiae, and christina loosestrife herb, and it can disperse and rectify the depressed liver-energy, activate blood circulation to dissipate blood stasis, clear heat and dry dampness, and soften and resolve hard mass [9].

A controlled study on patients with HBC indicates that Jieyu Ruanjian Huoxue prescription can markedly improve the TCM syndrome scores and hepatic function indices after intervention, and delay the progression of cirrhosis, which demonstrates a remarkable efficacy [10]. A study on patients with compensated cirrhosis revealed that Jieyu Ruanjian Huoxue prescription can significantly improve splenohepatomegaly and quality of life of patients, and the long-term outcome is worthy of recognition [11]. Currently, there are multiple studies on the intervention effects of Jieyu Ruanjian Huoxue prescription on patients with cirrhosis, yet few studies on changes in hepatic fibrosis indices have been reported. This study explored the influences of Jieyu Ruanjian Huoxue prescription on hepatic fibrosis indices and aspartate aminotransferase to platelet ratio index (APRI) in patients with HBC, so as to provide a clinical reference for improvement of the prognosis of patients with HBC.

Materials and methods

General data

A total of 140 patients with HBC who received treatment in our hospital from January 2019 to December 2019 were selected as the research subjects, and were divided into the study group (n=80, conventional treatment combined with Jieyu Ruanjian Huoxue prescription) and the control group (n=60, conventional treatment) based on different intervention methods.

Inclusion criteria: (1) the included subjects all met the diagnostic criteria for HBC [12] and were confirmed by laboratory examination; (2) those with good compliance; (3) those who

signed the informed consent. This study has been submitted to the Ethics Committee of The First People's Hospital of Fuyang Hangzhou for approval and implementation.

Exclusion criteria: (1) patients with a history of mental illness; (2) those complicated with malignant tumors; (3) those complicated with other virus infections; (4) those with disordered coagulation system; (5) pregnancy or lactation; (6) allergic to study drugs.

Rejection criteria: (1) loss to follow-up; (2) voluntary withdrawal during the investigation.

Intervention methods

The control group received conventional treatment (e.g., hepatoprotection, diuresis, anti-inflammation treatment and treatment of hepatitis B virus infection), and was treated with drugs (Entecavir and Diammonium Glycyrrhizinate).

The study group received Jieyu Ruanjian Huoxue prescription combined with conventional treatment. The prescription was composed of 30 g of *Salvia miltorrhiza*, 30 g of *Astragalus membranaceus*, 20 g of christina loosestrife herb, 20 g of Chinese Gentian, 20 g of stir-baked *Plastrum Testudinis* before treated with vinegar, 20 g of Tonkin Sophora Root, 20 g of stir-baked *Carapax Triongcis* with sand then treated with vinegar, 12 g of common oyster shell, 12 g of wenchow turmeric root tuber, 12 g of lightyellow sophora root, 10 g of peach seed, and 10 g of yanhusuo tuber, and 10 g of Costusroot, which were decocted with water to obtain a 300-400 mL of decoction. The decoction was taken twice in the morning and evening. One dose of decoction was taken daily for 12 weeks.

Observational indices and assessment criteria

Differences in clinical efficacies between the two groups: At 12 weeks after intervention, the clinical efficacies in the two groups were evaluated. The clinical efficacy was classified as marked response, moderate response and no response. Marked response: patients show obviously improved clinical symptoms and basically disappeared signs, their hepatic function indices and hepatic fibrosis indices basically return to normal, and imaging examination results reveal no liquid anechoic area after

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intervention. Moderately response: patients show improved clinical symptoms, hepatic function indices and hepatic fibrosis indices after intervention. No response: patients show insignificantly improved clinical symptoms and laboratory indices after intervention [13]. Overall response rate (ORR) = (marked response + moderate response)/total number of cases × 100%.

Analysis of changes in indices of hepatic fibrosis, hepatic function and inflammatory factors in the two groups: The two groups were followed up for 6 months. Before intervention and at 0, 1, 2, 3, 4, 5 and 6 months after intervention, the levels of hyaluronic acid (HA) and Type IV collagen (IV-C) in the two groups were recorded. The HA level was detected by chemiluminescence method, while IV-C level was determined by radioimmunoassay. The detection was performed using the automated biochemistry analyzer, and the kits were purchased from Aidikang Biochemical Reagent Co., Ltd., and the operations were carried out strictly in accordance with the instructions of the kits. Each index was continuously tested for 3 times and averaged as the final result. The hepatic function indices [aspartate aminotransferase (AST), alanine aminotransferase (ALT) and APRI] were evaluated in the two groups before intervention and at 6 months after intervention. The detection was performed using the automated biochemistry analyzer, and the matching reagents were used. The indices of inflammatory factors [interleukin-2 (IL-2) and tumor necrosis factor-alpha (TNF- α)] were evaluated using the enzyme-linked immunosorbent assay (ELISA) before intervention and at 6 months after intervention. The kits were purchased from Shanghai Jingkang Bioengineering Co., Ltd., and the operations were performed strictly in accordance with the instructions of the kits.

Correlation analysis of hepatic fibrosis indices and hepatic function indices: The correlation between hepatic fibrosis indices (HA, IV-C) and hepatic function indices (AST, ALT and APRI) was analyzed using Pearson correlation analysis.

Statistical method

The collected data statistically analyzed using SPSS 22.0. The enumeration data were repre-

sented by [n (%)]. The differences between groups were analyzed using chi-square test. The measurement data were represented by mean \pm standard deviation. The differences between groups were analyzed using t test. Student's t test was used for difference of continuous variables. The correlation between hepatic fibrosis indices and hepatic function indices was analyzed using Pearson correlation analysis. $P < 0.05$ indicated a statistically significant difference, and the study graphs were plotted using Graphpad Prism 8.0 [14].

Results

Comparison of differences in general data between the two groups

A total of 140 patients were enrolled, including 85 males and 55 females aged 39-63 years, with an average age of (46.00 \pm 3.21) years. Among the 60 patients in the study group, there were 37 males and 23 females. Among the 50 patients in the control group, there were 28 males and 22 females. The baseline data (e.g., gender, age, average course of disease, AST, ALT) were compared, and the result showed no statistically significant difference between the two groups ($P > 0.05$), which were comparable (**Table 1**).

Comparison of differences in clinical efficacies of interventions between the two groups

At 12 weeks after intervention, the clinical efficacies in the two groups were evaluated. The results showed that there were 70 patients with marked response, 9 patients with moderate response and 1 patient with no response, with the ORR of 98.75% in the study group, while there were 45 patients with marked response, 10 patients with moderate response and 5 patients with no response, with the ORR of 91.67% in the control group. The study group was superior to the control group in the ORR ($P < 0.05$) (**Table 2**).

Analysis of changes in hepatic fibrosis indices in the two groups during intervention

During the 6-month intervention, the hepatic fibrosis indices (HA and IV-C) in the two groups were dynamically analyzed, and the results suggested that there was no marked difference in HA and IV-C between the two groups before

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Table 1. Comparison of general clinical indices between the two groups ($\chi \pm s$)/[n(%)]

General clinical data		Study group (n=80)	Control group (n=60)	t/X ²	P
Gender	Male	49	32	0.881	0.348
	Female	31	28		
Average age (year)		46.33±2.32	45.98±2.41	0.869	0.386
Average weight (kg)		65.59±3.44	65.69±3.29	0.173	0.863
Mean course of disease (years)		1.29±0.71	1.31±0.68	0.168	0.867
AST (U/L)		78.98±8.21	79.18±7.98	0.209	0.835
ALT (U/L)		54.39±3.11	55.01±2.88	1.205	0.23
APRI		9.18±1.21	9.21±1.19	0.146	0.884
HA (ng/ml)		544.28±13.21	551.28±10.21	3.41	0.001
IV-C (ng/ml)		90.19±12.11	89.98±14.11	0.095	0.924
IL-2 (μg/L)		40.19±3.44	39.98±3.53	0.353	0.725
TNF-α (ng/L)		19.29±2.32	19.43±2.11	0.367	0.714

Table 2. Comparison of clinical efficacies between the two groups [n (%)]

Groups	Number of cases	Marked response	Moderate response	No response	ORR
Study group	80	70 (87.50)	9 (11.25)	1 (1.25)	79 (98.75)
Control group	60	45 (75.00)	10 (16.67)	5 (8.33)	55 (91.67)
X ²	-	-	-	-	4.194
P	-	-	-	-	0.041

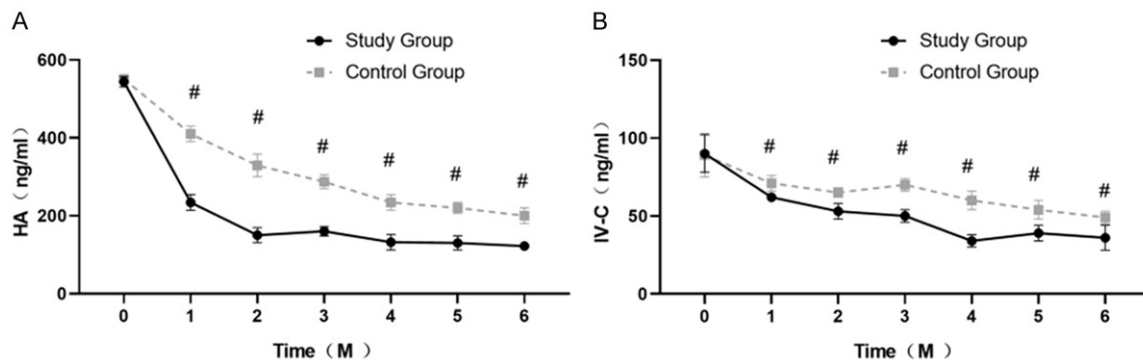


Figure 1. Analysis of changes in hepatic fibrosis indices in the two groups during the intervention. There was no marked difference in the levels of HA (A) and IV-C (B) between the two groups before intervention ($P > 0.05$). After intervention, the levels of HA and IV-C in the study group were noticeably lower than those in the control group at 1-6 months after intervention ($P < 0.05$). #indicates a statistically significant difference in the same indices at the same time points between the two groups.

intervention ($P > 0.05$). The comparison of dynamic indices demonstrated that the levels of HA and IV-C in the study group were higher than those in the control group during the 6-month intervention ($P < 0.05$) (**Figure 1**).

Analysis of changes in hepatic function indices between the two groups before and after intervention

Before intervention and at 6 months after intervention, the hepatic function indices (AST, ALT

and APRI) in the two groups were tested and evaluated, and the differences in the hepatic function indices between the two groups were compared. The results revealed that there was no statistically significant difference in the levels of AST and ALT and APRI between the two groups before intervention ($P > 0.05$). At 6 months after intervention, the comparison between the two groups demonstrated that the levels of AST and ALT and APRI in the two groups were remarkably reduced compared with those before intervention ($P < 0.05$). The

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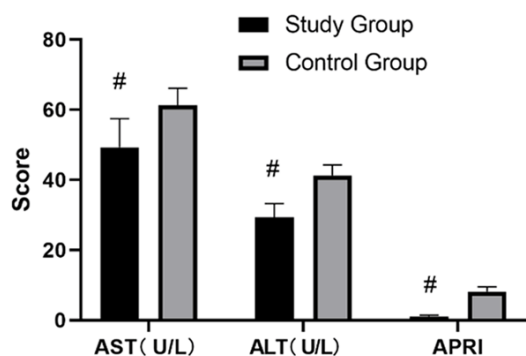


Figure 2. Analysis of changes in hepatic function indices between the two groups before and after intervention. The levels of AST and ALT and APRI in the study group were significantly lower than those in the control group ($P < 0.05$). #indicates a statistically significant difference in the same indices between the two groups.

comparison between groups exhibited that the levels of ALT and AST and APRI in the study group were lower than those in the control group after intervention ($P < 0.05$) (**Figure 2**).

Analysis of changes in inflammatory factors in the two groups before and after intervention

Before intervention and at 6 months after intervention, the levels of IL-2 and TNF- α were detected, and the differences in the levels of IL-2 and TNF- α were compared between the two groups. The results revealed that there was no statistically significant difference in the levels of IL-2 and TNF- α between the two groups before intervention ($P > 0.05$). At 6 months after intervention, the levels of inflammatory factors in the two groups were significantly reduced compared with those before intervention ($P < 0.05$). The comparison between groups after intervention demonstrated that the levels of IL-2 and TNF- α in the study group were lower than those in the control group ($P < 0.05$) (**Figure 3**).

Correlation analysis of hepatic fibrosis indices and hepatic function indices in patients with HBC

The analysis of the correlation between hepatic fibrosis indices (HA and IV-C) and hepatic function indices (AST, ALT and APRI) in patients with HBC exhibited that HA and IV-C were positively correlated with AST, ALT and APRI. Among them, IV-C was the most positively correlated with ALT ($r=0.9371$, $P < 0.05$), while HA was the

least positively correlated with AST ($r=0.8610$, $P < 0.05$) (**Figure 4**).

Discussion

HBV infection is a global epidemic disease [15]. Data show that about 350 million people are chronically infected with HBV, and up to 1 million people die of HBV-related diseases every year [16]. China is a high prevalence area of HBV infection. According to the seroepidemiological data of hepatitis B in 2006, the number of HBV carriers has reached 93 million in China, including about 25 million patients with chronic hepatitis B, and hepatitis B has become one of the three most important infectious diseases in China [17]. HBV infection can affect the immune response of the body and decline its immune function, which leads to the prolonged HBV infection and develops into chronic infection. If such patients fail to receive effective treatment, the probability of developing hepatitis B virus-related cirrhosis is about 0.4% to 14.2%, which results in a significant decrease in liver function [18, 19].

TCM has been used for diagnosis and treatment of hepatitis B. TCM believes that cirrhosis belongs to the category of “accumulation” and “abdominal mass”, and it occurs in the liver. The etiology and pathogenesis of cirrhosis include stagnation of liver Qi, asthenia of both the spleen and kidney, and stagnation of blood stasis caused by damp heat and the remaining poisonous influence, thus resulting in mass. According to TCM syndrome differentiation, the therapeutic principle of activating blood circulation to dissipate blood stasis, clearing heat and drying dampness, and softening and resolving hard mass should be adhered [20, 21]. In this study, the influences of Jieyu Ruanjian Huoxue prescription on hepatic fibrosis indices and APRI in patients with HBC were investigated. The results demonstrated that the ORR in the study group was remarkably higher than that in the control group (98.75% vs. 91.67%), suggesting that conventional treatment combined with Jieyu Ruanjian Huoxue prescription exhibited a more satisfactory efficacy. A previous study revealed that the ORR in patients with cirrhosis receiving conventional treatment combined with Yu Ruanjian Huoxue prescription was markedly higher than that in patients with cirrhosis receiving conventional western drugs (98.00%

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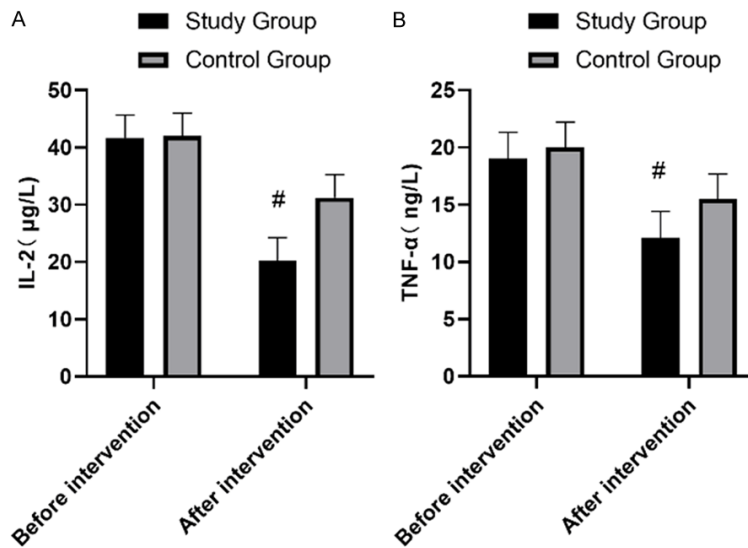


Figure 3. Analysis of changes in inflammatory factors in the two groups before and after intervention. There was no statistically significant difference in the levels of IL-2 (A) and TNF- α (B) between the two groups before intervention ($P > 0.05$). After intervention, the comparison between groups suggests that the levels of IL-2 and TNF- α in the study group were notably lower than those in the control group ($P < 0.05$). #indicates a statistically significant difference in the same indices between the two groups before and after intervention.

vs. 80.00%) [22], which is similar to the results of this study. A retrospective analysis of patients with decompensated cirrhosis indicated that Jieyu Ruanjian Huoxue prescription combined with adefovir dipivoxil significantly improved the clinical symptoms of patients with cirrhosis, and the dynamic evaluation on the patients after intervention demonstrated that their quality of life was noticeably improved [23]. In this study, Jieyu Ruanjian Huoxue prescription was composed of *Astragalus membranaceus*, yanhusuo tuber, red peony root, Christina loosestrife herb, Chinese Gentian, and lightyellow sophora root. Among them, *Astragalus membranaceus* can invigorate Qi for strengthening superficies, promote urination and tonify the heart, and eliminate bacteria and expel toxin. *Salvia miltorrhiza* can induce menstruation to stop pain, clear away heart fire and relieve restlessness, and cool blood and treat boils. Christina loosestrife herb can clear heat and remove toxicity, promote urination and expel stone, and activate blood flow and remove blood stasis. Chinese Gentian can remove liver-gallbladder fire, and clear heat and dry dampness. The combined use of the aforementioned drugs can remarkably improve the syndrome of stagnation of liver Qi in

patients with cirrhosis, so as to improve the clinical symptoms of the patients [24].

The authors believe that HBV infection can lead to desmoplasia in the liver and formation of incommas, thus causing deformed and hardened liver, and eventually resulting in cirrhosis. The progressive hepatic fibrosis is the main pathogenesis. The collagens in hepatic tissues occur around the central veins of liver and portal area in the physiological state. When cirrhosis occurs, there is a marked increase in the number of collagens, and collagens accumulate in the vascular pool and are finally transformed into fibroblasts, and fibrosis occurs [25]. In this study, the levels of HA and IV-C in the two groups before inter-

vention were higher than those after intervention, which conformed with previous results. After intervention, the hepatic fibrosis indices in the study group decreased significantly, exhibiting that the concomitant medication noticeably improved the levels of HA and IV-C and effectively controlled or improved the patients' conditions, which are similar to the results as previous reported [26]. To date, multiple studies have proved that cirrhosis is closely related to the immunologic mechanism of the body. In a study, the inflammatory factor level is used as an indicator for evaluation of conditions of patients with cirrhosis [27]. In this study, the levels of IL-2 and TNF- α in the study group were significantly lower than those in the control group after intervention, indicating that Jieyu Ruanjian Huoxue prescription could relieve symptoms of patients with cirrhosis through improving the inflammatory state.

In summary, Jieyu Ruanjian Huoxue prescription can remarkably improve the hepatic fibrosis, abnormal hepatic function, and the levels of inflammatory factors in patients with HBC, exhibiting a satisfactory efficacy. Therefore, Jieyu Ruanjian Huoxue prescription is worthy of clinical promotion and implementation. The

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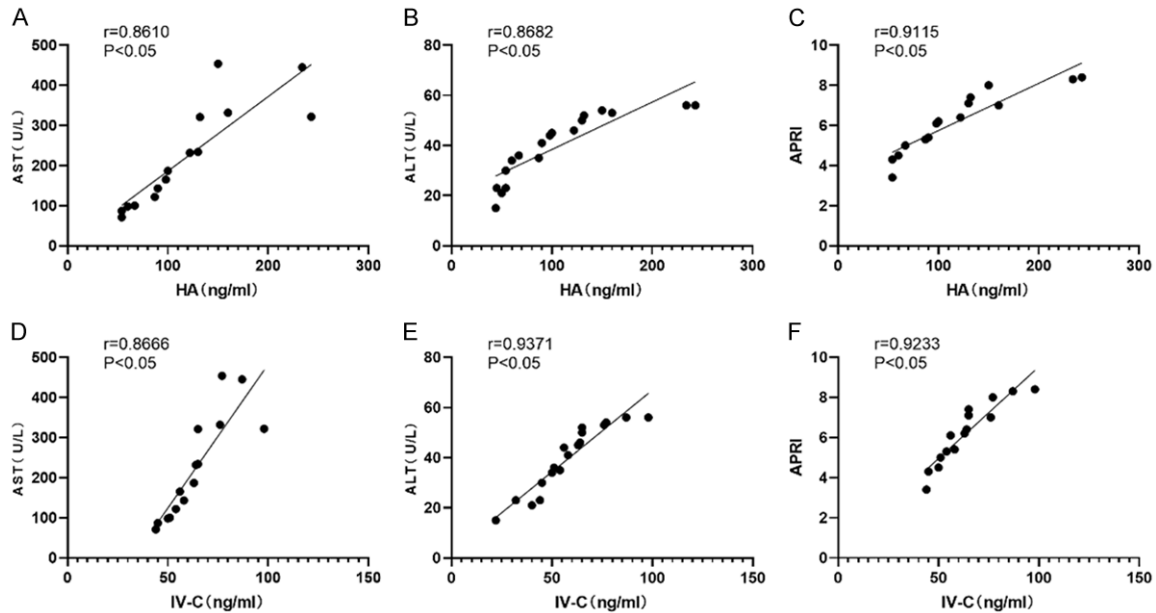


Figure 4. Correlation analysis of hepatic fibrosis indices and hepatic function indices in patients with HBC. The correlation analysis exhibited that HA and IV-C were positively correlated with AST (A and D), ALT (B and E) and APRI (C and F) in patients with HBC ($P < 0.05$). Among them, IV-C was the most significantly correlated with ALT ($r=0.9371$, $P < 0.05$) (E).

innovation of this study lies in demonstrating the influences of Jieyu Ruanjian Huoxue prescription on hepatic fibrosis indices and APRI in patients with HBC through comparison based on the detailed data, providing a theoretical reference for follow-up studies. The deficiency of this study is that one the one hand, the number of cases included in this study is small; one the other hand, the source of cases is relatively single, which affects the results to some extent. It is planned to carry out a large sample and multi-center investigation in the next step, so as to provide more detailed theoretical support for the research results.

Disclosure of conflict of interest

None.

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