Original Article

The regularity of nourishing-yin prescription for treating ascites due to hepatitis B cirrhosis based on data mining technology

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Background: Clinically, Chinese medicine is mostly used to treat ascites due to hepatitis B cirrhosis by nourishing-yin. We summarize the pattern of prescriptions for nourishing-yin inascites due to hepatitis B cirrhosis based on data mining to better use traditional Chinese medicine (TCM) to treat cirrhotic ascites in hepatitis B.

Methods: Articles published from 2000 to 2020 on ascites due to hepatitis B cirrhosis were searched in the Chinese National Knowledge Infrastructure and Chinese Science and Technology Journal Database. The results of the search were screened and then treated as the data sources in turn. Based on the data sources, a prescription database of ascites due to hepatitis B cirrhosis was constructed. The data mining was conducted by statistical analysis of frequency and association. Core herbs, including the property and flavor, channel tropism, regularities of medicinal recipes, and core sets, among others, were examined.

Results: Through combing 199 articles, a total of 201 prescriptions were selected, involving 138 kinds of herbs. The efficacy of cold herbs was slightly higher than that of warm herbs. The main flavors of herbs were sweet, bitter, and pungent. There were 30 herbs used ≥26 times in 201 prescriptions. The highest frequency of use was *Poria cocos*, followed by *atractylodis macrocephalae*, and *radix astragali*. Ninety-nine commonly used drug combinations were obtained according to the association rules, of which there were 60 associated drug groups with a frequency ≥34, of which the highest frequency was *poria cocos-rhizoma atractylodis macrocephalae*, *poria cocos-oriental water plantain rhizome*, *poria cocos-radix astragali*. Frequent medicinal recipes consisted largely of medicines for tonifying deficiency, including diuretics for eliminating dampness, medicines for promoting blood circulation and removing blood stasis, and supplements for clearing heat and regulating qi.

Conclusions: Through data mining, it was found that when TCM treats ascites due to hepatitis B cirrhosis, it attaches importance to using methods of tonifying deficiency and invigorating spleen for diuresis based on nourishing-yin to improve the clinical efficacy, which can provide reference for TCM's clinical use of nourishing-yin to treat ascites due to hepatitis B cirrhosis.

Keywords: Hepatitis B cirrhosis; ascites; deficiency of yin; nourishing-yin recipe; cluster analysis

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Introduction

Hepatitis B cirrhosis, caused by the hepatitis B virus (HBV), is a chronic progressive liver disease. Hepatitis B cirrhosis results in diffuse liver disease due to the effect of prolonged or repeated action of one or multiple etiologies (1). It is estimated that 240 million people worldwide experience chronic HBV, and approximately 2% to 4% of patients develop compensated cirrhosis without effective treatment each year (2). Microscopically, cirrhosis shows absolute attenuation of the normal hepatocytes, massive fibrous hyperplasia, and nodule formation (3). Macroscopically, cirrhosis shows decreased volume atrophy in the liver (4). Cirrhosis is theoretically described as a "tympanite" disease in traditional Chinese medicine (TCM). In *Suwen·Yinyang Yingxiang Dalun*, cirrhosis was described as "yang transforming qi and yin transforming shape". Therefore, cirrhosis is the embodiment of yin deficiency. The etiology and pathogenesis of cirrhosis can mostly be attributed to deficiency in the origin and excess in superficiality. Tonifying deficiency is the common treatment principle in treatment for cirrhosis in TCM (5).

Ascites is one of the most common complications of cirrhosis. Refractory ascites is present in 15–20% of all patients with ascites. Refractory ascites brings repeated hospitalizations, severe reduction in quality of life, and even death for patients (6). Therefore, it is particularly important to actively prevent the occurrence and development of cirrhotic ascites at an early stage.

Highlight box

Key findings

- Dispersion, elimination, and invigoration should all be applied in the treatment process of yin deficiency.

What is known and what is new?

- Approximately 1.5% to 4% of patients with cirrhosis further develop decompensated liver cirrhosis each year (with symptoms of ascites, hepatic encephalopathy, gastrointestinal varices, and hemorrhage, among others).
- This study used the Auxiliary Platform for Traditional Chinese Medicine Inheritance to analyze the literature related to nourishing-yin prescription for hepatitis B cirrhosis-related ascites over the past 20 years. A reference basis was subsequently provided for the clinical treatment of ascites due to hepatitis B cirrhosis.

What is the implication, and what should change now?

- All results of this study aim to provide theoretical basis for the clinical treatment of ascites due to hepatitis B cirrhosis.

TCM classifies patients with post-hepatitis B cirrhosis into "liver-kidney yin deficiency", "dampness-heat internal smoldering", "stasis-heat internal smoldering", "liver depression and spleen deficiency", and "spleen-kidney qi deficiency" (7). "Yin deficiency" is defined as a pathophysiological state with yin-related dysfunction (8). In the early stages of ascites due to hepatitis B cirrhosis, most of the symptoms of yin deficiency are not obvious, so yin deficiency is easily ignored in the process of treatment. However, in the late stage of hepatitis B cirrhosis-related ascites, yin deficiency is aggravated. Nourishing yin can easily invigorate the spleen for diuresis, while invigorating the spleen for diuresis can damage yin at this time (9). The treatment of late-stage hepatitis B cirrhosis-related ascites is difficult, as the disease is prone to variation and a threat to the life of patients. It has been proposed in TCM that Shaoyang-Taiyin syndrome is the basic pathogenesis of ascites from hepatitis B cirrhosis. Congestion and water stagnation are the symptoms of the occurrence of Shaoyang-Taiyin disease. Yin deficiency is an important pathological factor of ascites due to hepatitis B cirrhosis. In the treatment of ascites due to hepatitis B cirrhosis, the "reconciliation and Shaoyang" method and "warming Taiyin" are radical therapies, and promoting blood circulation and disinhibiting water are symptomatic treatments (10). In recent years, a large number of studies have proved that Chinese medicine has significant clinical effects and fewer side effects in the treatment of ascites due to hepatitis B cirrhosis, but the clinical ideas and medication habits of various scholars and physicians vary, and there are many experiences in the treatment of ascites due to hepatitis B cirrhosis, which are inconvenient to learn and pass on better (11,12). In order to optimize the treatment of ascites due to hepatitis B cirrhosis, we used the Auxiliary Platform for Traditional Chinese Medicine Inheritance (Institute of Traditional Chinese Medicine, Chinese Academy of Traditional Chinese Medicine, China) to analyze the composition of nourishing-yin prescription in the literature of hepatitis B cirrhosis-related ascites in the past 20 years. In this way, a reference basis for the clinical treatment of ascites due to hepatitis B cirrhosis was created.

Methods

Source and screening of prescriptions

Articles published from the year 2000 to 2020 related to ascites due to hepatitis B cirrhosis were searched in the

Chinese National Knowledge Infrastructure (CNKI 2.0) and the Chinese Science and Technology Journal Database (CSTJ). The search terms for the first search were as follows: "ascites", "peritoneal effusion", and "tympanites". The search terms for the second search were as follows: "yin", "jing", "blood", "liquid", and "jin". The subject headings, keywords, and abstracts of each paper were combined to conduct a cross search. Tracing and querying were subsequently performed for the references of the target literature and review literature. This yielded 174 articles related to the treatment of ascites due to hepatitis B cirrhosis with the method of nourishing yin, which were then manually screened. This resulted in 198 complete prescriptions from the screened articles. The search terms for the second search were changed to "experience", which yielded 25 articles about the treatment of ascites due to hepatitis B cirrhosis as summarized by prominent TCM doctors. After the articles were read one by one, 3 prescriptions about the treatment of ascites due to hepatitis B cirrhosis with the method of nourishing yin were selected. Finally, through combing 199 articles, a total of 201 target prescriptions were obtained. Inclusion and exclusion criteria were as follows. Inclusion criteria: (I) the disease diagnosis in the literature was clearly ascites from hepatitis B cirrhosis; the TCM certificate type included Yin deficiency. (II) The type of literature was clinical observation with effective treatment results, medical cases or experience summary of TCM experts. (III) There were clear prescriptions, flavors and dosages of herbal medicines in the literature. Exclusion criteria: (I) the prescription, flavor and dosage of Chinese medicine in the literature were incomplete; (II) duplicate literature and the same prescriptions in different literature.

Database establishment

First, a database was established with Microsoft Excel. Downloaded the medical case entry template provided by the TCM inheritance computing platform, entered the prescription data that met the inclusion criteria according to the template requirements, and standardized the terms involved in the prescriptions: deleted the method of concoction from the Chinese medicine drug names. For example, "*processed rhizoma pinelliae*" and "*rhizoma pinellinae praeparata*" were uniformly entered as "*pinellia ternata*" and modified according to the platform requirements with reference to the Pharmacopoeia of the People's Republic of China (2015 edition) (13). The data was individually reviewed by two team members and timely proofread for incorrect information to ensure data authenticity and accuracy and reduce bias. After the entry was completed, the excel file was uploaded to the TCM inheritance computing platform to establish the database.

Data entry and analysis methods

The screened prescriptions were then entered with the help of the Auxiliary Platform for Traditional Chinese Medicine Inheritance. The specific steps for data entry were as follows: (I) the established database was uploaded in the "Data Upload" module of the software. (II) After "Statistical Analysis" in the "Data Analysis" module was run, "Four Properties (cold, hot, warm, and cool) (14)", "Five Flavors (sour, sweet, bitter, pungent, and salty) (15)", "Channel Tropism", and "Efficiency" were analyzed, and the results of analysis were exported. (III) The "Herb Frequency", "Association Rule", and "Cluster Analysis" in the "Analysis of Prescription" modules were each entered. In "Association Rule", Set the "Number of Support" (the numbers of occurrences of the same herbs at the same time among all herbs), and "Confidence Level", and export results. In "Cluster Analysis", cluster analysis [the core algorithm, including the improved mutual information method and complex system entropy cluster (2,5)] was conducted. Before cluster analysis, the number of clusters was selected. The "Extraction and Combination" command was then executed to perform network display [the basic algorithm was unsupervised entropy hierarchical clustering (16-18)]. Finally, the related results were exported one by one.

Results

Property, flavor, channel tropism, and efficacy statistics of the medicines in prescriptions

A total of 201 prescriptions were included. Property, flavor, channel tropism, and efficacy statistics of all medicines were recorded. According to the results, most of the medicines in prescriptions were cold, with a sweet flavor, placing them in the liver channel (*Table 1*). Most of the cold herbs belonged to tonifying herbs (36.3%) (*Figure 1*), suggesting TCM treatment of ascites due to hepatitis B cirrhosis was mainly based on tonifying deficiency.

Frequency statistics of herb used in prescriptions

The frequency of the herbs used in 201 prescriptions were

Table 1 Regularities of property, flavor, and channel tropism of medicines in prescriptions

Category	Classification frequency (times)
Four gases	
Cold	1,004
Warm	712
Neutral	657
Cool	89
Hot	16
Five flavors	
Sweet	1,625
Bitter	1,049
Pungent	553
Salty	177
Sour	166
Channel tropism	
Liver	1,142
Spleen	1,120
Kidney	1,019
Lung	993
Heart	755
Stomach	655
Bladder	310
Small intestine	172
Large intestine	155
Gall bladder	152
Triple energizer	30
Pericardium	1

further determined. The frequency of herbs appearing ≥26 times is shown in *Table 2*. *Poria cocos*, *rhizoma atractylodis macrocephalae*, *and radix astragali* were applied frequently. *Poria cocos* could clear damp-heat, which had spleen-fortifying effects; rhizoma atractylodis macrocephalae focused on percolating water and resolving dampness; and radix astragali could invigorate qi for strengthening superficies. The results above indicated that TCM treatment of ascites due to hepatitis B cirrhosis consisted primarily of tonifying deficiency and invigorating the spleen for diuresis.

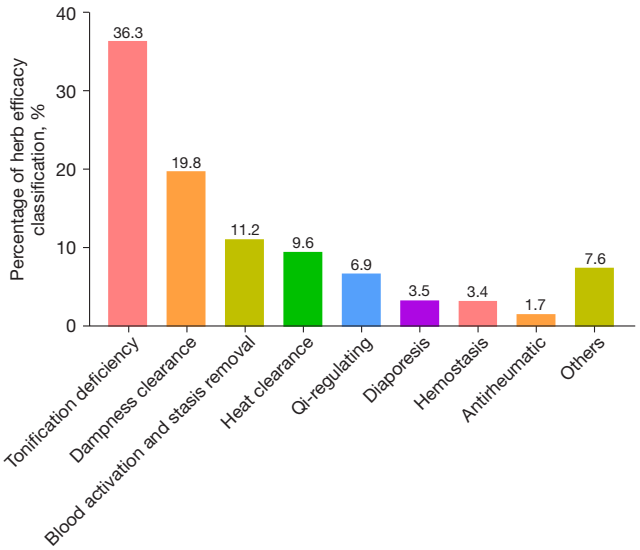

Figure 1 Classification frequency diagram of herb efficacy.

Prescription regularities analysis based on association rules

A total of 99 common herb combinations were obtained according to association rules. The associated herb groups that appeared ≥34 times are shown in *Table 3*. The combination of poria cocos-rhizoma atractylodis macrocephalae and poria cocos oriental water plantain rhizome occurred with a high frequency. The association of herb combinations (confidence level ≥0.76) in prescriptions was further examined. It was found that the confidence level of oriental water plantain rhizome-radix rehmanniae *recens-poria cocos*, *radix astragali oriental water plantain rhizome-radix salviae miltiorrhizae-poria cocos*, and *cassia twig-poria cocos* was close to 1 (*Table 4*). The confidence level of the above herb combinations indicated that the prescriptions mainly contained the herbs for tonifying deficiency and invigorating spleen for diuresis. These results suggested that *poria cocos*, *radix astragali*, and *rhizoma atractylodis macrocephalae* were the most common compatible herbs.

Prescription regularities analysis based on an unsupervised clustering algorithm (k means) and regression analysis

According to the unsupervised clustering algorithm (k means), the prescriptions underwent cluster analysis. After further regression analysis, 5 core herb combinations were found (*Figure 2*). All 5 core herb combinations contained 6 herbs (*Table 5*), with the efficacy related to nourishing yin, soothing liver, and invigorating spleen for diuresis.

Table 2 Herbs appearing ≥26 times in prescriptions

Order	Herb name	Frequency
1	Poria cocos	136
2	Rhizoma atractylodis macrocephalae	113
3	Radix astragali	100
4	Oriental water plantain rhizome	98
5	Grifola	92
6	Carapax trionycis	82
7	Radix salviae miltiorrhizae	79
8	Radix angelicae sinensis	76
9	Radix rehmanniae recens	76
10	Pericarpium arecae	73
11	Radices paeoniae alba	59
12	Radix ophiopogonis	59
13	Adenophora stricta miq	50
14	Semen plantaginis	50
15	Radix codonopsis	50
16	Fructus lycii	50
17	Radix paeoniae rubra	48
18	Rhizoma dioscoreae	47
19	Radix glycyrrhizae	40
20	Radix bupleuri	37
21	Cassia twig	37
22	Herba lycopi	35
23	Radix pseudostellariae	34
24	Rhizoma imperatae	34
25	Fructus ligustri lucidi	33
26	Herba artemisiae scopariae	31
27	Colla corii asini	30
28	Fructus corni	28
29	Concha ostreae	26
30	Endothelium corneum gigeriae galli	26

Discussion

HBV is a hepatotropic virus, and within TCM, it is a type of damp-heat epidemic virus. After invading the human body, HVB directly enters the liver and remains there for a long time, causing liver damage. Zheng *et al.* showed that HBV damaged and consumed body liquid, causing hepatic yin injury (19). The kidney is a water viscus, with the function of storing essence. However, the liver and kidney are present together in the lower energizer, exchanging essence and blood between each other. The liver and kidney share a common source, so when liver damage occurs, there is often concomitant kidney damage. Che *et al.* (20) thought that liver and kidney yin deficiency were the core pathogenesis in deficiency in origin and excess in superficiality and "coexistence of blood stasis and deficiency" for post hepatitis cirrhosis. In TCM, it is thought that ascites due to hepatitis B cirrhosis is a deficiency in origin and excess in superficiality; specifically, the deficiency of the liver, spleen, and kidney is the origin, while qi stagnation, blood stasis, and retained fluid is the superficiality (21,22). Ascites, one of the common complications of hepatitis B cirrhosis, is difficult to treat and characterized by frequent recurrence and high mortality (23). At present, the treatment of Western medicine for ascites consists mainly of diuretics, with poor efficacy and considerable side effects. Patients with ascites due to hepatitis B cirrhosis accompanied by deficiency in the liver, spleen, and kidney, are also prone to a deficiency in systemic yin fluid. A related study has revealed that, compared with Western medicine, the treatment of TCM for ascites due to hepatitis B cirrhosis has clear advantages (24).

Deficiency of the liver, spleen, and kidney is the predominant etiology in patients with ascites due to hepatitis B cirrhosis. Clinically, patients with severe ascites and abdominal distension are prone to experiencing complicating hydrothorax, especially right pleural effusion. Based on systemic qi and blood, the heart stores the spirit. Deficiency of qi and blood can result in loss of mind. Moreover, pathogenic factors like phlegm-heat syndrome, damp-heat, and others can blind the mind and heart, causing obnubilation and hepatic coma. Based on the theory of the liver governing free coursing, the liver can help the stomach digest food. In this study, we found that the frequencies of cold herbs were higher than those of warm herbs in clinical prescriptions. Sweet, bitter, and pungent were the main flavors of the herbs. Herbs with a sweet flavor can tonify deficiency and so are applied at high frequencies. Herbs with a bitter flavor can nourish yin and clear heat. Herbs with pungent flavor can promote qi and activate blood as well as eliminate stagnation and activate meridians. The combination of herbs of different natures and flavors can strengthen healthy qi and eliminate pathogenic factors. The efficacy of herbs examined in this

Table 3 The associated herb groups appearing ≥34 time in prescriptions

Order	Associated herb groups	Occurrence frequency
1	Poria cocos, rhizoma atractylodis macrocephalae	88
2	Poria cocos, oriental water plantain rhizome	84
3	Poria cocos, radix astragali	72
4	Poria cocos, grifola	72
5	Rhizoma atractylodis macrocephalae, radix astragali	70
6	Oriental water plantain rhizome, grifola	62
7	Rhizoma atractylodis macrocephalae, oriental water plantain Rhizome	62
8	Rhizoma atractylodis macrocephalae, grifola	58
9	Poria cocos, radix salviae miltiorrhizae	57
10	Poria cocos, rhizoma atractylodis macrocephalae, radix astragali	56
11	Poria cocos, carapax trionycis	56
12	Rhizoma atractylodis macrocephalae, radix salviae miltiorrhizae	55
13	Rhizoma atractylodis macrocephalae, carapax trionycis	54
14	Radix astragali, radix salviae miltiorrhizae	54
15	Poria cocos, radix rehmanniae recens	53
16	Poria cocos, radix angelicae sinensis	53
17	Rhizoma atractylodis macrocephalae, pericarpium arecae	53
18	Poria cocos, oriental water plantain rhizome, grifola	53
19	Poria cocos, rhizoma atractylodis macrocephalae, oriental water plantain rhizome	52
20	Radix astragali, carapax trionycis	51
21	Radix astragali, oriental water plantain rhizome	51
22	Radix astragali, grifola	49
23	Radix astragali, pericarpium arecae	48
24	Poria cocos, pericarpium arecae	48
25	Poria cocos, rhizoma atractylodis macrocephalae, radix salviae miltiorrhizae	46
26	Poria cocos, rhizoma atractylodis macrocephalae, grifola	46
27	Poria cocos, radix astragali, oriental water plantain rhizome	45
28	Poria cocos, radix astragali, radix salviae miltiorrhizae	43
29	Radix rehmanniae recens, radix ophiopogonis	43
30	Poria cocos, rhizoma atractylodis macrocephalae, carapax trionycis	43
31	Rhizoma atractylodis macrocephalae, radix angelicae sinensis	43
32	Carapax trionycis, radix salviae miltiorrhizae	42
33	Oriental water plantain rhizome, radix salviae miltiorrhizae	41
34	Poria cocos, radix astragali, carapax trionycis	41
35	Poria cocos, radix codonopsis	41

Table 3 (*continued*)

Table 3 (*continued*)

Order	Associated herb groups	Occurrence frequency
36	Oriental water plantain rhizome, pericarpium arecae	41
37	Rhizoma atractylodis macrocephalae, radix astragali, radix salviae miltiorrhizae	41
38	Rhizoma atractylodis macrocephalae, oriental water plantain rhizome, grifola	40
39	Rhizoma atractylodis macrocephalae, radix astragali, carapax trionycis	40
40	Grifola, carapax trionycis	40
41	Poria cocos, rhizoma atractylodis macrocephalae, pericarpium arecae	39
42	Poria cocos, radices paeoniae alba	39
43	Poria cocos, radix astragali, grifola	39
44	Rhizoma atractylodis macrocephalae, radix astragali, oriental water plantain rhizome	39
45	Oriental water plantain rhizome, carapax trionycis	38
46	Poria cocos, semen plantaginis	38
47	Rhizoma atractylodis macrocephalae, radix astragali, grifola	38
48	Rhizoma atractylodis macrocephalae, radix astragali, pericarpium arecae	37
49	Poria cocos, oriental water plantain rhizome, radix salviae miltiorrhizae	37
50	Radix salviae miltiorrhizae, pericarpium arecae	36
51	Rhizoma atractylodis macrocephalae, radix paeoniae rubra	36
52	Poria cocos, rhizoma atractylodis macrocephalae, radix astragali, radix salviae miltiorrhizae	36
53	Grifola, pericarpium arecae	36
54	Radix astragali, radix angelicae sinensis	35
55	Poria cocos, rhizoma atractylodis macrocephalae, radix astragali, carapax trionycis	35
56	Poria cocos, cassia twig	35
57	Grifola, radix rehmanniae recens	35
58	Rhizoma atractylodis macrocephalae, radix codonopsis	35
59	Poria cocos, rhizoma dioscoreae	35
60	Radix astragali, carapax trionycis, radix salviae miltiorrhizae	34

study was mainly related to toxification deficiency, and the combination of herbs included diuretics for eliminating dampness, medicines for promoting blood circulation and removing blood stasis, and supplements for clearing heat and regulating qi. The efficacy of the above herbs was consistent with the treatment method of ascites due to hepatitis B cirrhosis.

Zan *et al.* (25) suggested that the disease position of ascites due to cirrhosis in the spleen, liver, kidney, and the spleen was the major position. Therefore, the treatment of ascites due to cirrhosis relies mainly on strengthening the spleen. Chen *et al.* (26) posited that in the lesion process of ascites due to cirrhosis, the key to the lesion is the spleen, with the main etiology being the insufficiency of the spleen. In this study, the 2 herbs with the highest frequencies were poria cocos and rhizoma atractylodis macrocephalae. Poria cocos and rhizoma atractylodis macrocephalae are the major components of Lishui formulas like Wuling powder, Lingguizhugan decoction, and other medicines. The herbs above are the common herbs in the treatment of ascites due to hepatitis B cirrhosis for invigorating spleen for diuresis. Li *et al.* (27) believe that the deficiency of vital energy,

Table 4 The associations of herb combinations in prescriptions (confidence level ≥0.76)

Order	Associations	Associations	Confidence level
1	Oriental water plantain rhizome, radix rehmanniae recens	Poria cocos	0.97
2	Radix astragali, oriental water plantain rhizome, radix salviae miltiorrhizae	Poria cocos	0.97
3	Cassia twig	Poria cocos	0.95
4	Oriental water plantain rhizome, radix salviae miltiorrhizae	Poria cocos	0.9
5	Grifola, radix rehmanniae recens	Poria cocos	0.89
6	Oriental water plantain rhizome, carapax trionycis	Poria cocos	0.89
7	Radix astragali, oriental water plantain rhizome	Poria cocos	0.88
8	Rhizoma atractylodis macrocephalae, radix astragali, carapax trionycis	Poria cocos	0.88
9	Rhizoma atractylodis macrocephalae, radix astragali, radix salviae miltiorrhizae	Poria cocos	0.88
10	Oriental water plantain rhizome	Poria cocos	0.87
11	Rhizoma atractylodis macrocephalae, radix astragali, oriental water plantain rhizome	Poria cocos	0.87
12	Radix astragali, radix angelicae sinensis	Rhizoma atractylodis macrocephalae	0.86
13	Poria cocos, radix astragali, carapax trionycis	Rhizoma atractylodis macrocephalae	0.85
14	Rhizoma atractylodis macrocephalae, oriental water plantain rhizome, grifola	Poria cocos	0.85
15	Oriental water plantain rhizome, grifola	Poria cocos	0.85
16	Radix glycyrrhizae	Poria cocos	0.85
17	Rhizoma atractylodis macrocephalae, oriental water plantain rhizome	Poria cocos	0.84
18	Rhizoma atractylodis macrocephalae, radix salviae miltiorrhizae	Poria cocos	0.84
19	Poria cocos, radix astragali, radix salviae miltiorrhizae	Rhizoma atractylodis macrocephalae	0.84
20	Poria cocos, oriental water plantain rhizome, radix salviae miltiorrhizae	Radix astragali	0.84
21	radix codonopsis	Poria cocos	0.82
22	Rhizoma atractylodis macrocephalae, Radix astragali, grifola	Poria cocos	0.82
23	Poria cocos, radix salviae miltiorrhizae	Rhizoma atractylodis macrocephalae	0.81
24	Carapax trionycis, radix salviae miltiorrhizae	Radix astragali	0.81
25	Poria cocos, pericarpium arecae	Rhizoma atractylodis macrocephalae	0.81
26	Poria cocos, rhizoma atractylodis macrocephalae, carapax trionycis	Radix astragali	0.81
27	Cassia twig	Grifola	0.81
28	Cassia twig	Oriental water plantain rhizome	0.81
29	Radix astragali, radix salviae miltiorrhizae	Poria cocos	0.8
30	Oriental water plantain rhizome, pericarpium arecae	Poria cocos	0.8
31	Radix astragali, carapax trionycis	Poria cocos	0.8
32	Rhizoma atractylodis macrocephalae, radix astragali	Poria cocos	0.8
33	Oriental water plantain rhizome, pericarpium arecae	Rhizoma atractylodis macrocephalae	0.8

Table 4 (*continued*)

Table 4 (*continued*)

Order	Associations	Associations	Confidence level
34	Rhizoma atractylodis macrocephalae, carapax trionycis	Poria cocos	0.8
35	Radix astragali, grifola	Poria cocos	0.8
36	Rhizoma atractylodis macrocephalae	Poria cocos	0.79
37	Poria cocos, radix astragali, grifola	Rhizoma atractylodis macrocephalae	0.79
38	Rhizoma atractylodis macrocephalae, grifola	Poria cocos	0.79
39	Grifola, carapax trionycis	Poria cocos	0.78
40	Grifola, radix astragali	Rhizoma atractylodis macrocephalae	0.78
41	Radix astragali, carapax trionycis	Rhizoma atractylodis macrocephalae	0.78
42	Poria cocos, rhizoma atractylodis macrocephalae, radix salviae miltiorrhizae	Radix astragali	0.78
43	Radix astragali, grifola	Rhizoma atractylodis macrocephalae	0.78
44	Grifola	Poria cocos	0.78
45	Oriental water plantain rhizome, radix salviae miltiorrhizae	Radix astragali	0.78
46	Rhizoma atractylodis macrocephalae, radix angelicae sinensis	Poria cocos	0.77
47	Radix astragali, pericarpium arecae	Rhizoma atractylodis macrocephalae	0.77
48	Poria cocos, carapax trionycis	Rhizoma atractylodis macrocephalae	0.77
49	Carapax trionycis, radix salviae miltiorrhizae	Poria cocos	0.76
50	Semen plantaginis	Poria cocos	0.76

blood stasis, and fluid retention throughout each period of tympanites is the major etiology. Deficiency of vital energy is the initiating and aggravating factor of tympanites. Fan *et al.* (28) proposed that promoting blood circulation for removing blood stasis plays a key part in Lishui and should be continued throughout the whole process of treatment for ascites due to hepatitis B cirrhosis. Zhao *et al.* pointed out that the symptom of ascites due to hepatitis B cirrhosis was ascites while the disease sources were located in the blood. The stagnation of blood stasis is the basic contradiction of ascites due to hepatitis B cirrhosis (29). Ma *et al.* (30) reported that Jianpi Huoxue Lishui decoction could treat ascites due to hepatitis B cirrhosis and could improve the liver function of patients. In the present study, the associated herb groups of poria cocos-rhizoma atractylodis macrocephalae-grifola-oriental water plantain rhizome and poria cocos-rhizoma atractylodis macrocephalae-radix astragali could invigorate the spleen for diuresis and nourish and tonify blood, which was consistent with previous studies.

(I) *Rhizoma dioscoreae-poria cocos-oriental water plantain rhizome-fructus corni-cortex moutan-radix rehmanniae preparata* (combination 1) is the core combination of the prescription of Liuwei Dihuang pills with the function of nourishing-kidney yin. The above core combination of herbs can be applied for the treatment of deficiency of kidney-yin characterized by soreness and weakness of waist and knees as well as hot flashes and night sweat. (II) *Rhizoma atractylodis macrocephalae-radix astragali-poria cocos-pericarpium arecae-carapax trionycis-radix salviae miltiorrhizae* (combination 2) is the combination that can invigorate spleen for diuresis, nourish yin, and soften hard mass as well as nourish blood and promote blood circulation. Pericarpium arecae can lower qi and eliminate turgor, which is more valuable for the treatment of ascites due to hepatitis B cirrhosis with the symptom of abdominal distension. (III) *Rhizoma atractylodis macrocephalae-poria cocos-radix astragali-pericarpium arecae-grifola-oriental water plantain rhizome* (combination 3) is a herb combination that can tonify qi and invigorate the spleen for diuresis. Poria cocos, grifola, and oriental water plantain rhizome can promote urination, which can treat patients with severe ascites due to hepatitis

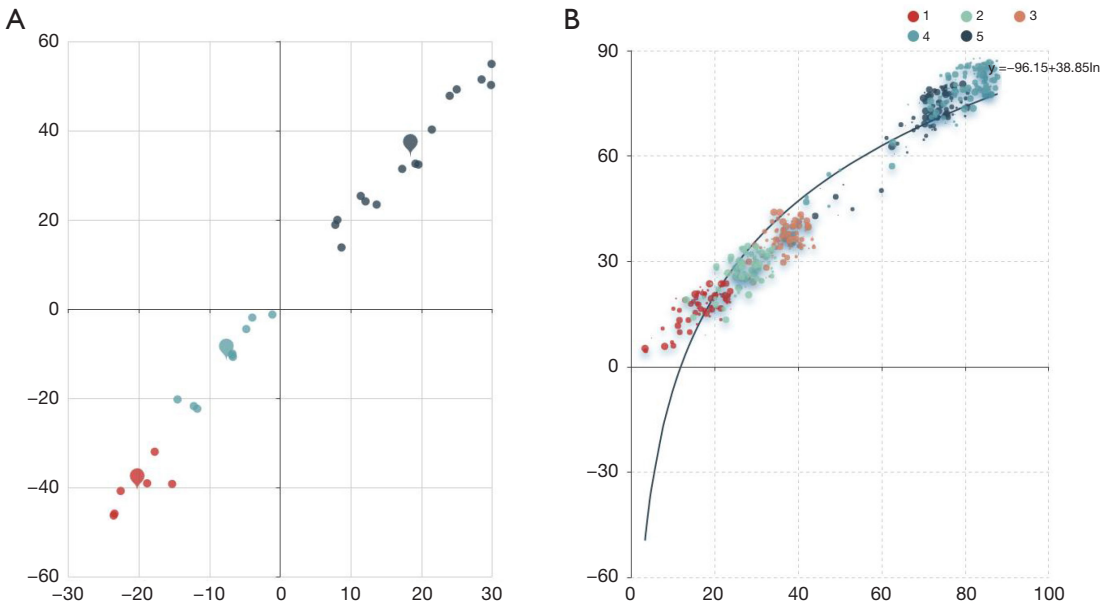

Figure 2 Regression analysis simulation diagram for prescription frequency. (A) Cluster analysis diagram for the prescriptions. (B) Simulation diagram for k means and regression analysis. 1= combination 1, *Rhizoma dioscoreae-poria cocos-oriental water plantain rhizome-fructus corni-cortex moutan-radix rehmanniae preparata*; 2= combination 2, *Rhizoma atractylodis macrocephalae-radix astragali-poria cocos-pericarpium arecae-carapax trionycis-radix salviae miltiorrhizae*; 3= combination 3, *Rhizoma atractylodis macrocephalae-poria cocos-radix astragali-pericarpium arecae-grifola-oriental water plantain rhizome*; 4= combination 4, *Rhizoma atractylodis macrocephalae-cocos-radix astragali-carapax trionycis-radix salviae miltiorrhizae-oriental water plantain rhizome*; 5= combination 5, *Radix ophiopogonis-radix rehmanniae recens-adenophora stricta miq-poria cocos-grifola-fructus lycii*.

Table 5 Herb core combinations based on unsupervised clustering algorithm (k means)

Combination	Core combinations	Frequencies
1	Rhizoma dioscoreae, poria cocos, oriental water plantain rhizome, fructus corni, cortex moutan, radix rehmanniae preparata	23
2	Rhizoma atractylodis macrocephalae, radix astragali, poria cocos, pericarpium arecae, carapax trionycis, radix salviae miltiorrhizae	32
3	Rhizoma atractylodis macrocephalae, poria cocos, radix astragali, pericarpium arecae, grifola, oriental water plantain rhizome	23
4	Rhizoma atractylodis macrocephalae, poria cocos, radix astragali, carapax trionycis, radix salviae miltiorrhizae, oriental water plantain rhizome	75
5	Radix ophiopogonis, radix rehmanniae recens, adenophora stricta miq, poria cocos, grifola, fructus lycii	48

B cirrhosis. (IV) *Rhizoma atractylodis macrocephalae-cocos-radix astragali-carapax trionycis-radix salviae miltiorrhizae-oriental water plantain rhizome* (combination 4) has a high cluster frequency. Compared with core combination 2, combination 4 replaces pericarpium arecae with *oriental water plantain rhizome*. *Oriental water plantain rhizome* can promote urination, clear damp-heat, and eliminate kidney zang turbidity, which are described in *New Compilation of Materia Medica*. *Oriental water plantain rhizome* can be applied for the treatment of patients with ascites due to hepatitis B cirrhosis. (V) *Radix ophiopogonis-radix rehmanniae recens-adenophora stricta miq-poria cocos-grifola-fructus lycii* (combination 5). The core combination above belongs to the prescription of Yiguanjian decoction, which can nourish

hepatic yin and invigorate spleen for diuresis. Combination 5 is consistent the treatment principles of ascites due to hepatitis B cirrhosis.

Conclusions

Deficiency of yin is an important pathological factor for ascites due to hepatitis B cirrhosis. Dispersion, elimination, and invigoration should be all applied in the treatment process of deficiency of yin. Healthy energy is supported mainly by the combination with upper, middle, and lower energizers (triple energizers). Based on qi-blood-water, multiple visceral functions can be fully used to adjust qi movement and smooth the blood and body liquid. Overall, the results of this study aim to provide a theoretical basis for the clinical treatment of ascites due to hepatitis B cirrhosis.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-23-883/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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