Comparative Analysis of Clinical and Medication Information between Chronic Hepatitis B Patients with Damp Heat Syndrome and Spleen Deficiency Syndrome

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1.Introduction

Hepatitis B is caused by hepatitis B virus (HBV) infection. At present, the prevalence of hepatitis B surface antigen (HBsAg)-positive is about 4.9% worldwide [1]. China has a high incidence of hepatitis B. It is estimated that the prevalence of HBV infection in the general population of China is 5%−7.99% [2]. About 50% patients with HCC were complicated with HBV infection [3]; the Global Hepatitis Report 2017 shows that approximately 887 thousand people die of chronic hepatitis B- (CHB-) related complications worldwide in 2015, mainly due to liver cirrhosis and hepatocellular carcinoma. To prevent the prognosis of CHB, early diagnosis and effective treatment are very important.

The current treatment of CHB is mainly antiviral drugs, which can effectively block the replication of HBV-DNA and reduce the incidence of cirrhosis and HCC [4]. Traditional Chinese medicine (TCM) is widely used in China; it has the advantages of early treatment and combined intervention in the treatment of hepatitis B, which is reported to be beneficial for alleviating liver damage, reducing jaundice, regulating immunity [5], and inhibiting the development of liver fibrosis and HCC. TCM also was reported to lower the risk of death among CHB patients with contaminant liver cirrhosis and...
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improvement of ALT (Figure 1).

We recorded the changes in the syndrome of these patients, and drugs that promote bile excretion of the DH syndrome were significantly higher than those of the SD syndrome (\(p < 0.002\), respectively). The age and AFP values of patients with DH syndrome were slightly higher than those of patients with SD syndrome, but there was no statistical difference (Table 1). To assess the effect of drugs on differences in liver function, we compared the clinical medications of the two groups of patients. There was no difference in the composition of antiviral drugs, Chinese herbal medicine, and antifibrosis proprietary Chinese medicine between DH syndrome and SD syndrome. However, the proportion of immunomodulators in the DH syndrome group was significantly higher than that in the SD syndrome group (\(P < 0.05\)). And the proportion of hepatoprotective drugs and drugs that promote bile excretion of the DH syndrome was slightly higher than that in the SD syndrome (\(P < 0.1\), Table 1).

2. Methods

2.1. Study Design. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5), and were approved by the IRB of Shuguang Hospital affiliated to Shanghai University of Traditional Chinese Medicine (Permit Number: 2012-206-22-01). Informed consent was obtained from all patients for being included in the study. This is a cross section study based on 2079 unidentified individual-level data from the database collected from 2008 to 2015, which consisted of two parts. The first data set contained 999 CHB patients with TCM syndrome differentiation records in the database; we described the distribution of syndrome types and compared the general information, clinical indicators, and drug usage between CHB patients with DH syndrome and SD syndrome. Among the patients in the first data set, 207 CHB patients were followed up after 3 months to form data set 2. We recorded the changes in the syndrome of these patients, compared the clinical indicators and medication information, and analyzed the related risk factors that affect the improvement of ALT (Figure 1).

2.2. Inclusion and Exclusion Criteria of Participants. Patients who met the diagnostic criteria of "chronic hepatitis B" [15] according to the "China Guidelines for Prevention and Treatment of Chronic Hepatitis B (2005)" [16], aged from 18 to 65, and signed informed consent were included. Patients who had viral hepatitis, chronic severe hepatitis, severe primary diseases, or mental diseases or were pregnant women or lactating women were excluded. The standard of the TCM syndrome differentiation was according to the "TCM Syndrome Differentiation Standard of Viral Hepatitis" [17] and "The Clinical Research Guide of New Drugs of Traditional Chinese Medicine" [18]; detailed syndrome differentiation standards are attached in Additional file 2.

2.3. Statistics. We used SPSS (version 26.0) for all statistical analyses. Shapiro–Wilk test was used to assess data normality. We evaluated the numerical variables that did not violate normality test and homogeneity test of variance by T-test, while the remaining numerical variables were compared using the Mann–Whitney U-test, and categorical data adopted the \(\chi^2\) test. The normal distribution variables were expressed as mean \(\pm\) standard deviation (\(x \pm s\)); the non-normal distribution variables were expressed using the median (median (1/4 quantile, 3/4 quantile)). The correlation analysis was estimated by the logistic regression. Simple logistic regression was conducted to estimate crude odds ratios (OR) and their 95% confidence intervals (95% CI) for all factors related to ALT differences. Multiple logistic regression was used to adjust potential confounding by age, gender, and other drug use. The differences were considered significant at \(P < 0.05\).

3. Results

3.1. Comparison of Clinical Indexes and Medication of CHB Patients with DH Syndrome and SD Syndrome at Baseline. Among the 999 CHB patients, the proportion of DH syndrome was the highest (%), followed by the SD syndrome (\(n = 429\)) or SD syndrome (\(n = 383\)) to analyze the clinical indexes differences. The ALT, AST, TBA, and PT values of the DH syndrome were significantly higher than those of the SD syndrome (\(P = 0.048, P = 0.024, P = 0.006, P = 0.002\), respectively). The age and AFP values of patients with DH syndrome were slightly higher than those of patients with SD syndrome, but there was no statistical difference (Table 1). To assess the effect of drugs on differences in liver function, we compared the clinical medications of the two groups of patients. There was no difference in the composition of antiviral drugs, Chinese herbal medicine, and antifibrosis proprietary Chinese medicine between DH syndrome and SD syndrome. However, the proportion of immunomodulators in the DH syndrome group was significantly higher than that in the SD syndrome group (\(P < 0.05\)). And the proportion of hepatoprotective drugs and drugs that promote bile excretion of the DH syndrome was slightly higher than that in the SD syndrome (\(P < 0.1\), Table 1).
3.2. Comparison of Clinical Indexes and Drug Use among the Four Main TCM Syndrome Conversion Groups in CHB Patients after 3-Month Follow-Up. Among the 232 CHB patients who were followed up after 3 months, the composition ratio of syndrome changes after 3 months is shown in Figure 1(b). Among the 130 patients diagnosed with DH syndrome for the first time, 96 (73.84%) patients maintained the DH syndrome unchanged (group A), and 25 (19.23%) patients changed from DH syndrome to SD syndrome after 3 months (group B). Among the 101 patients diagnosed with SD syndrome at the first time point, 46 (45.54%) patients changed to DH syndrome after 3 months of follow-up (group C), and 40 (39.60%) patients maintained the SD syndrome unchanged (group D).

We compared the dynamic differences in clinical indicators between patients with syndrome changes and those with unchanged syndromes. As seen in Table 2, there was no significant difference in gender, age, and medication between patients in groups C and D. Compared with group C, the improvement of TBIL, AST, and ALB in group D was more significant (P < 0.05), and the improvement trend of ALT, APRI, and FIB-4 in group D was slightly better than that in group C (P < 0.1). The results indicate that CHB patients with SD syndrome who converted into DH
Table 1: Baseline analysis of 812 CHB patients with DH syndrome and the SD syndrome.

|                        | DH (n = 429) | SD (n = 383) | Statistics | P   |
|------------------------|--------------|--------------|------------|-----|
| **Gender (male, %)**   | 326 (75.99%) | 213 (55.61%) | 0.889<sup>a</sup> | 0.346 |
| **Age (years)**        | 44.44 (37.1, 54.61) | 44.06 (36.22, 51.38) | -1.887 | 0.059 |
| **Treatment**          |              |              |            |     |
| Antiviral therapy      | 259 (60.37%) | 231 (60.31%) | 0.000<sup>a</sup> | 0.986 |
| Recent anti-virus<sup>*</sup> | 60 (23.34%) | 51 (22.76%) | 0.023<sup>a</sup> | 0.881 |
| Antivirus duration (days) | 325 (60.13%) | 370.5 (101, 1074.5) | -1.378 | 0.168 |
| Hepatoprotective drugs | 15 (3.49%) | 4 (1.04%) | 5.324<sup>a</sup> | 0.021 |
| Immunomodulator        |              |              |            |     |
| Drugs that promote bile excretion | 46 (10.72%) | 28 (7.31%) | 2.844<sup>a</sup> | 0.092 |
| Chinese herbal medicine | 108 (25.65%) | 99 (25.84%) | 0.048<sup>a</sup> | 0.826 |
| Anti-fibrosis proprietary Chinese medicine | 18 (4.19%) | 21 (5.48%) | 0.733<sup>a</sup> | 0.392 |
| Untreated              | 81 (18.88%) | 70 (18.27%) | 0.049<sup>a</sup> | 0.825 |
| **Liver function value** |            |              |            |     |
| TBIL (μmol/L)          | 16.6 (12.5, 22.47) | 15.7 (12.47, 21.08) | -1.119 | 0.263 |
| DBIL (μmol/L)          | 4.4 (3.3, 6.7) | 4.4 (3.03, 6.3) | -0.994 | 0.32 |
| ALT (U/L)              | 36 (26.02, 60.75) | 33 (24, 56) | -2.25 | 0.024 |
| AST (U/L)              | 29.85 (18, 65.5) | 28 (17.77, 55.25) | -1.352 | 0.176 |
| ALP (U/L)              | 79 (64, 100) | 75.15 (63, 96) | -1.617 | 0.106 |
| ALB (g/L)              | 45.5 (43, 47.8) | 45.4 (42.62, 48.1) | -0.315 | 0.753 |
| Pre-Alb (g/L)          | 241 (178, 290) | 237.35 (180, 288.5) | -0.043 | 0.966 |
| TBA (μmol/L)           | 7.6 (3.9, 14) | 7.9 (2.9, 12.8) | -2.749 | 0.006 |
| **Hepatitis B virus**  |              |              |            |     |
| HBeAg positive (%)     | 227 (53.53%) | 186 (49.33%) | 1.410<sup>a</sup> | 0.235 |
| HBV-DNA (IU/mL)        | 13020 (0, 2270000) | 7181 (0, 2115000) | -1.245 | 0.213 |
| **Liver fibrosis value** |            |              |            |     |
| APRI                   | 0.48 (0.31, 0.91) | 0.46 (0.27, 0.80) | -1.429 | 0.153 |
| FIB-4                  | 1.63 (1.07, 2.77) | 1.52 (1.01, 2.33) | -1.603 | 0.109 |
| **Other biomarkers**   |              |              |            |     |
| PT (S)                 | 13.2 (12.2, 14.4) | 12.7 (12, 13.9) | -3.054 | 0.002 |
| AFP (ng/mL)            | 3.67 (2.6, 6.5) | 3.45 (2.36, 5.84) | -1.845 | 0.065 |
| CD4/CD8                | 1.33 (1.02, 1.76) | 1.26 (0.89, 1.73) | -1.641 | 0.101 |
| **Lipids, Blood glucose** |            |              |            |     |
| FBG (mmol/L)           | 5.18 (4.85, 5.47) | 5.14 (4.85, 5.5) | -0.601 | 0.548 |
| TC (mmol/L)            | 4.59 (3.83, 5.2) | 4.58 (3.96, 5.22) | -0.891 | 0.373 |
| TG (mmol/L)            | 1.1 (0.82, 1.49) | 1.07 (0.79, 1.52) | -0.281 | 0.779 |
| HDL-C (mmol/L)         | 1.18 (1, 1.415) | 1.2 (1.01, 1.43) | -0.666 | 0.506 |
| LDL-C (mmol/L)         | 2.54 (2.02, 2.94) | 2.46 (2.11, 3.05) | -0.611 | 0.541 |
| **Blood routine test** |              |              |            |     |
| WBC (10<sup>9</sup>/L) | 5.01 (4.26, 6.01) | 5 (4.13, 6.04) | -0.259 | 0.796 |
| LY (10<sup>9</sup>/L)  | 1.64 (1.28, 2) | 1.68 (1.32, 2.04) | -0.656 | 0.512 |
| MONO (10<sup>9</sup>/L) | 0.31 (0.24, 0.4) | 0.32 (0.26, 0.41) | -0.769 | 0.442 |
| NEUT (10<sup>9</sup>/L) | 2.89 (2.25, 3.6) | 2.8 (2.16, 3.65) | -0.749 | 0.454 |
| PLT (10<sup>9</sup>/L)  | 159 (124, 202.5) | 159 (122, 198) | -0.151 | 0.88 |
| **Renal function value** |            |              |            |     |
| BUN (mmol/L)           | 4.48 (3.61, 5.2) | 4.37 (3.6, 5.11) | -0.718 | 0.473 |
| Cr (μmol/L)            | 70 (59.78, 80) | 68 (60, 78) | -1.253 | 0.21 |
| UA (μmol/L)            | 300 (256.5, 354) | 303.5 (244, 352) | -0.37 | 0.712 |

<sup>*The time interval between the start date of antiviral treatment and the enrollment date ≤ 90 days. APRI = (AST (U/L)/upper limit of normal value (U/L))/PLT (×10<sup>9</sup>/L) ×100; FIB-4 = age (year) × AST (U/L)/(PLT (×10<sup>9</sup>/L) × ALT (U/L)<sup>1/2</sup>).</sup>

syndrome have a worse clinical recovery of liver function than those who maintained SD syndrome, which is consistent with the trend of liver damage in the first cross-sectional observation. Although no significant difference was found in the clinical indicator comparison between group A and group B, the CHB patients who have maintained DH syndrome had a worse liver function trend than those of SD syndrome patients. In terms of medication, the untreated patient in group A was significantly higher than that in group B, and the proportion of taking Chinese herbal medicine in group A was significantly lower than that in group B. An additional file shows this in more detail (see Additional file 1).

3.3. Analysis of the Factors Related to the Improvement of ALT Level in CHB Patients. We used the logistic regression model to analyze whether TCM syndrome is a variable closely
related to a different recovery of serum ALT. Since the serum ALT level of most patients in the follow-up after 3 months was lower than the first time point, we used whether the ALT decreased more than 30% from the baseline level during the follow-up after 3 months as the dependent variable. To exclude the interference of the syndrome conversion, CHB patients in group A or group D whose serum ALT level was abnormal (more than 50U/L) at baseline were included in the model (including 49 patients in group A and 24 patients in group D). Simple logistic regression analysis was used to include syndrome grouping and medication information as independent variables. DH syndrome is a significant negative factor (OR [95% CI]: 4.854 [1.149–20.501], \( P = 0.032 \)). Then, we used the multiple logistic regression model, which included age, gender, and HBV-DNA value as covariates; the adjusted OR value of DH syndrome was 4.936 (\( P = 0.032 \)). These results indicate that DH syndrome is a negative factor for reducing the serum ALT level in CHB patients (Table 3).

4. Discussion

In this study, we analyzed clinical data of 999 CHB patients with TCM syndrome records. Among these patients, DH syndrome and SD syndrome were the two most common syndromes, accounting for 81.72% of the total collected CHB patients, which was consistent with previous research.

| Table 2: Comparison of clinical index difference and medication between group C and group D. |
|---------------------------------|----------------|----------------|----------------|
|                                | Group C (SD to DH) n = 46 | Group D (sustained SD) n = 40 | Statistics | \( P \) |
| Gender (male, %)               | 32 (69.56%) | 32 (80%) | 1.224\(^a\)   | 0.269 |
| Age (years)                    | 41.64 (36.54, 51.49) | 48.48 (37.64, 51.98) | −1.056      | 0.291 |
|                                |                |                |              |      |
| **Treatment**                  |                |                |              |      |
| Antiviral therapy             | 26 (56.52%) | 28 (70%) | 1.664\(^a\)   | 0.197 |
| Recent antivirus              | 10 (21.73%) | 9 (22.5%) | 0.007\(^a\)   | 0.932 |
| Antivirus duration (days)      | 116 (53.5, 515) | 173 (53.5, 416) | −0.090      | 0.928 |
| Hepatoprotective drugs        | 18 (39.13%) | 19 (47.5%) | 0.614\(^a\)   | 0.434 |
| Immunomodulator               | 0 (0%) | 0 (0%) | —            | —     |
| Drugs that promote bile excretion | 4 (8.69%) | 3 (7.5%) | 0.041\(^a\)   | 0.597 |
| Chinese herbal medicine       | 17 (36.95%) | 15 (37.5%) | 0.003\(^a\)   | 0.959 |
| Antifibrosis proprietary Chinese medicine | 1 (2.2%) | 3 (7.5%) | 1.369\(^a\)   | 0.257 |
| Untreated                      | 4 (8.69%) | 0 (0%) | 3.648\(^a\)   | 0.077 |
| **Liver function value**       |                |                |              |      |
| TBIL (\( \mu \)mol/L)         | 0.04 (−1.87, 3.14) | −1.6 (−6.65, 2.22) | −1.979      | 0.048 |
| DBIL (\( \mu \)mol/L)         | 0 (−0.7, 1) | 0 (−1.72, 1.12) | −0.792      | 0.428 |
| ALT (U/L)                      | −11 (−34, 5.75) | −19 (−96, −6.25) | −1.875      | 0.061 |
| AST (U/L)                      | −2 (−15.25, 9.75) | −12.5 (−69, 1) | −2.130      | 0.033 |
| GGT (U/L)                      | −1 (−23, 3) | −8.5 (−51, 3) | −1.178      | 0.239 |
| ALP (U/L)                      | 0.5 (−11.25, 8.25) | −3 (−13, 8.75) | −0.723      | 0.469 |
| ALB (g/L)                      | 1 (−2.32, 2.82) | 2.19 (0.05, 5.15) | −2.156      | 0.031 |
| Pre-Alb (g/L)                  | 0 (−112, 64.5) | 19 (−116.5, 70) | −0.004      | 0.996 |
| TBA (\( \mu \)mol/L)          | −2.3 (−5.05, 0.02) | −2.75 (−15.07, −0.27) | −1.130      | 0.258 |
| **Hepatitis B virus**          |                |                |              |      |
| HBcAg (S/CO)                   | −0.075 (−155.5925, 0.775) | −3.135 (−90.502, 0.385) | 0.444\(^a\)  | 0.505 |
| HBV-DNA (IU/mL)                | −35280 (−2775257, 643.75) | −25080.5 (−5387429.25, 0) | −0.320      | 0.749 |
| **Liver fibrosis value**       |                |                |              |      |
| FIB-4                          | 0.04 (−0.21, 0.36) | −0.22 (−0.86, 0.42) | −1.697      | 0.09  |
| APRI                           | −0.02 (−0.1826, 0.069) | −0.18 (−0.83, 0.02) | −1.939      | 0.052 |
| **Other biomarkers**           |                |                |              |      |
| PT (S)                         | −0.24 (−0.82, 0.52) | 0 (−0.75, 0.67) | −0.671      | 0.502 |
| AFP (ng/mL)                    | −1.13 (−3.50, 0.05) | −0.97 (−3.18, −0.05) | −0.089      | 0.929 |
| CD4/CD8                        | 0.06 (−0.18, 0.37) | 0.07 (−0.13, 0.31) | −0.320      | 0.749 |
| **Lipids, blood glucose**      |                |                |              |      |
| FBG (mmol/L)                   | −0.09 (−0.51, 0.06) | 0.24 (−0.03, 0.50) | −3.355      | 0.001 |
| TC (mmol/L)                    | −0.27 (−0.73, 0.13) | −0.32 (−1.30, 0.2) | −0.377      | 0.706 |
| TG (mmol/L)                    | −0.03 (−0.26, 0.13) | −0.08 (−0.57, 0.19) | −0.615      | 0.542 |
| HDL-C (mmol/L)                 | −0.16 ± 0.33 | −0.09 ± 0.51 | −0.818      | 0.416 |
| LDL-C (mmol/L)                 | −0.10 ± 0.69 | −0.31 ± 1.04 | 1.103       | 0.273 |
| **Blood routine test**         |                |                |              |      |
| WBC (10\(^{9}\)/L)             | 0.14 ± 1.19 | 0.39 ± 1.23 | −0.964      | 0.338 |
| LY (10\(^{9}\)/L)               | 0.04 ± 0.40 | 0.07 ± 0.53 | −0.306      | 0.76  |
| MONO (10\(^{9}\)/L)             | 0.01 (−0.10, 0.10) | −0.02 (−0.16, 0.08) | −0.737      | 0.461 |
| NEUT (10\(^{9}\)/L)             | 0.11 (−0.4, 0.71) | 0.55 (−0.19, 1.23) | −1.367      | 0.172 |
| PLT (10\(^{9}\)/L)              | −9.59 ± 27.25 | 5.63 ± 31.57 | −1.610      | 0.111 |
Persistent liver damage is more likely to be accompanied with HBV-related cirrhosis and hepatocellular carcinoma. In this study, the AFP level of patients with DH syndrome had a higher trend than that of the SD syndrome (Table 1, \( P = 0.065 \)). In the dynamic observation, the improvement trend of FIB-4 and APRI scores of patients with sustained SD syndrome showed also a better trend than patients with TCM syndrome converted from SD to DH (Table 2, \( P = 0.09 \) and \( P = 0.052 \), respectively), and there was no difference in the usage of antifibrosis drugs between the two groups. Studies also pointed out that CHB patients with DH syndrome were more likely to be complicated with hepatitis B cirrhosis and liver cancer. The hepatitis B cirrhosis patients with DH syndrome are distributed in Child–Pugh grades A, B, and C, but are mainly in the B and C grades and more prone to having complications, such as upper gastrointestinal hemorrhage and hepatic encephalopathy [23]. The DH syndrome (accounting for 30.97%) also was the most common type in the III stage of liver cancer [24]. Combined with our results, it is suggested that patients with CHB DH syndrome are associated with higher liver damage and potentially higher risk of liver fibrosis and hepatocellular carcinoma.

Medication also has a great effect on liver function, so we compared the difference in medication between the two groups of patients. In the first part of the cross-sectional study, CHB patients with DH syndrome had significantly higher level of ALT, AST, and TBA, but took more immunomodulators and hepatoprotective drugs than the SD syndrome group (\( P = 0.021 \) and \( P = 0.081 \)). In the second part of the dynamic follow-up observation, there was no difference between the medications of the patients in group C and group D, but the rate of taking traditional Chinese herbal medicine in group A was significantly lower than that in group B, and ALT had a poor improvement trend in group A (Additional file 1). Therefore, in order to further clarify the influence of syndromes and medication information on the improvement of ALT, we conducted the logistic analysis to screen for risk factors that affect the improvement of ALT. The regression analysis results showed that the decrease of ALT is related to the syndrome types; DH syndrome is an adverse effect on the reduction of ALT in CHB patients. However, due to the small difference in medication between the two groups, the drugs were not statistically significant in models.

The biological basis of CHB patients with DH syndrome having a higher level of ALT is still unclear; some researches suggest that the expression of inflammatory cytokines of CHB patients with DH syndrome is relatively higher and the immune response is hyperactive. The CHB patients with DH syndrome have potentially higher risk of liver fibrosis and hepatocellular carcinoma.
syndrome had a significantly higher level of serum MIP-1α than that of patients with liver-kidney yin deficiency syndrome [25]. In addition, the A allele proportion of TNF-α-308 gene in patients with DH syndrome of hepatitis B cirrhosis is significantly higher than that of non-DH syndrome [26]. Yinchenhao Decoction (YCHD) is a classic prescription for treating jaundice with DH syndrome. Network pharmacological studies have shown that YCHD can treat chronic liver diseases through functional modules such as immune response, inflammation, energy metabolism, and so on. However, compared with Huangqi decoction for qi deficiency syndrome, YCHD has unique functional modules related leptin-induced complement pathway and leukocyte migration across the endothelium, which may correlate with the anti-inflammatory effects [27].

5. Limitations
There are still some problems in this study. For example, this is a cross section study with a low level of evidence. The number of research cases is not enough, especially in the dynamic analysis. Therefore, we need to constantly expand the sample size to verify and modify the results.

6. Conclusion
In this study, we explored the clinical and medication differences of CHB patients with two common TCM. Based on the analysis of combined medication in the real world, we found that CHB patients with DH syndrome have potentially more serious and sustained liver function damage than those with SD syndrome. The DH syndrome is a negative factor for reducing serum ALT level in CHB patients. This study provides a reference for the personalized management and treatment of chronic hepatitis B patients from the perspective of TCM syndromes.

Data Availability
The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

Authors’ Contributions
Qiao-Hong Liu and Bin-Bin Zhang contributed equally to this work. Y Zhao and YY Hu conceived and designed the study. Y Zhao, L Xu, XP Shen, and YM Hai performed data collection. QH Liu and BB Zhang performed data analysis. QH Liu wrote the draft manuscript. Y Zhao revised the manuscript.

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Supplementary Materials
Additional file 1 (Supplementary Table 1. Comparison of clinical index difference and medication between group A and group B). Additional file 2 (Diagnostic criteria for damp-heat and spleen deficiency syndrome differentiation of CHB patients). (Supplementary Materials)

References
[1] Polaris Observatory Collaborators, “Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study,” The Lancet. Gastroenterology & Hepatology, vol. 3, no. 6, pp. 383–403, 2018.
[2] H. Wang, P. Men, Y. Xiao et al., “Hepatitis B infection in the general population of China: a systematic review and meta-analysis,” BMC Infectious Diseases, vol. 19, no. 1, p. 811, 2019.
[3] Y. Xie, “Hepatitis B virus-associated hepatocellular carcinoma,” Advances in Experimental Medicine and Biology, vol. 1018, pp. 11–21, 2017.
[4] World Health Organization, Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection, World Health Organization, Geneva, Switzerland, 2015.
[5] F. H. Qi, Z. X. Wang, P. P. Cai, L. Zhao, J. J. Gao, and N. Kokudo, “Traditional Chinese medicine and related active compounds: a review of their role on hepatitis B virus infection,” Drug Discoversies and Therapeutics, vol. 7, no. 6, pp. 212–223, 2013.
[6] T.-Y. Tsai, T.-H. Hung, H. Livneh, I.-H. Lin, M.-C. Lu, and C.-C. Yeh, “Chinese herbal medicine therapy and the risk of mortality for chronic hepatitis B patients with concurrent liver cirrhosis: a nationwide population-based cohort study,” Oncotarget, vol. 9, no. 26, pp. 18214–18223, 2018.
[7] T.-Y. Tsai, H. Livneh, T.-H. Hung, I.-H. Lin, M.-C. Lu, and C.-C. Yeh, “Associations between prescribed Chinese herbal medicine and risk of hepatocellular carcinoma in patients with chronic hepatitis B: a nationwide population-based cohort study,” BMJ Open, vol. 7, no. 1, Article ID e014571, 2017.
[8] L. Zhang, G. Wang, W. Hou, P. Li, A. Dulin, and H. L. Bonkovsky, “Contemporary clinical research of traditional Chinese medicines for chronic hepatitis B in China: an analytical review,” Hepatology, vol. 51, no. 2, pp. 690–698, 2010.
[9] X.-X. Zeng, Z.-X. Bian, T.-X. Wu, S.-F. Fu, E. Ziea, and W. T. C. Woon, “Traditional Chinese medicine syndrome distribution in chronic hepatitis B populations: a systematic review,” The American Journal of Chinese Medicine, vol. 39, no. 6, pp. 1061–1074, 2011.
[10] G. Mao, G. Cai, B. Chen, and L. Liao, “Distribution characteristics of TCM syndromes of chronic hepatitis B based on the clinical literature in the past five years,” Henan Tradit Chin Med (Henan Zhong Yi), vol. 36, no. 11, pp. 1931–1933, 2016, in Chinese.
[11] E.-L. Liu and X.-J. Wang, “Correlation between distribution of TCM syndromes and clinical test indicators based on 451 cases chronic viral hepatitis type B,” China Journal of Traditional Chinese Medicine and Pharmacy (Zhong Hua Zhong Yi Yao Za Zhi), vol. 34, no. 4, pp. 1793–1795, 2019, in Chinese.

[12] L. Zhang, H. Jiang, and H. Pan, “Relativity research on chronic hepatitis B TCM syndromes and clinical test indexes,” Journal of Zhejiang Chinese Medical University (Zhejiang Zhong Yi Yao Da Xue Xue Bao), vol. 36, no. 1, pp. 21-22, 2012, (in chinese).

[13] B. Chen, G. Mao, and G.-X. Cai, “Correlation between hepatobiliary damp-heat syndrome of chronic hepatitis B and ALT & TBil: a meta-analysis,” Chinese Journal of Integrated and Traditional West Medicine Liver Disorders (Zhongguo Zhong Xi Yi Jie He Gan Bing Za Zhi), vol. 24, no. 3, pp. 177–181, 2014, in Chinese.

[14] Q. Ma, “Correlation analysis between TCM Syndromes of chronic hepatitis B and clinical examination index,” Clinical Journal of Chinese Medicine (Zhong Yi Lin Chuang Yan Jiu), vol. 8, no. 3, pp. 22-23, 2016, in Chinese.

[15] A. S. F. Lok and B. J. McMahon, “Chronic hepatitis B,” Hepatology, vol. 45, no. 2, pp. 507–539, 2007.

[16] Chinese Society of Hepatology Chinese Medical Association, Chinese Society of Infectious Diseases, and Chinese Medical Association, “Guideline on prevention and treatment of chronic hepatitis B in China(2005),” Chinese Medical Journal (England), vol. 120, no. 24, pp. 2159–2173, 2007.

[17] Association Internal Medicine Hepatopathy Committee of Chinese Traditional Medicine, “The standards of TCM differential syndromes of viral hepatitis,” Traditional Chinese Medicine, vol. 5, pp. 39-40, 1992, in Chinese.

[18] X. Y. Zheng, Guideline for Clinical Research on New Chinese Medicine Drugs, Chinese Medical Sciences Technology, Beijing, China, 2002.

[19] G. Mao, G. Cai, and B. Chen, “The TCM syndrome distribution characteristic of 1868 chronic hepatitis B patients and the correlation analysis with virology indices of serum by logistic regression,” Journal of Traditional Hunan University of Chinese Medicine (Hunan Zhong Yi Yao Da Xue Xue Bao), vol. 34, no. 4, pp. 24-28, 2014, in Chinese.

[20] Y. Liu, “The study of relationship of traditional Chinese medicine type of syndrome of Autoimmune hepatitis and objective detective signs,” Master Dissertation, Guangzhou University of Chinese Medicine (Guangzhou Zhong Yi Yao Da Xue), 2016, in Chinese.

[21] L.-M. Gu, P.-R. Cao, C. Gu, L.-F. Wei, and Y.-Z. Tian, “Correlation between traditional Chinese medicine syndrome and clinical biochemical indexes of non-alcoholic fatty liver,” Journal of Nanjing University Traditional Chinese Medicine (Nanjing Zhong Yi Yao Da Xue Xue Bao), vol. 35, no. 6, pp. 738–740, 2019, in Chinese.

[22] M. G. Ghany, J. J. Feld, K.-M. Chang et al., “Serum alanine aminotransferase flares in chronic hepatitis B infection: the good and the bad,” The Lancet Gastroenterology & Hepatology, vol. 5, no. 4, pp. 406-417, 2020.

[23] C. Hu, “Correlation analysis of TCM syndrome types of hepatitis B cirrhosis and child-pugh classification,” Guangming Journal of Chinese Medicine (Guangming Zhong Yi), vol. 33, no. 4, pp. 465-466, 2018, in Chinese.

[24] G. Yang, “Study on diagnosis and treatment rule of primary liver cancer based on data mining,” Doctoral Dissertation, Hubei University of Chinese Medicine (Hubei Zhong Yi Yao Da Xue), 2019, in Chinese.

[25] Y.-Y. Lu, Y. Zhao, Y.-N. Song et al., “Serum cytokine profiling analysis for zheng differentiation in chronic hepatitis B,” Chinese Medicine, vol. 10, no. 1, p. 24, 2015.

[26] Z.-P. Shi, T.-Y. Wu, Y. Liu et al., “Research on the association between hepatitis B liver cirrhosis of dampness-heat syndrome and tumor necrosis factor-a gene polymorphism,” China Journal of Traditional Chinese Medicine and Pharmacy (Zhong Hua Zhong Yi Yao Za Zhi), vol. 29, no. 6, pp. 2004–2006, 2014, in Chinese.

[27] Z. Chen, X. Wang, Y. Li et al., “Comparative network pharmacology analysis of classical TCM prescriptions for chronic liver disease,” Frontiers in Pharmacology, vol. 10, p. 1353, 2019.