The Score Model Containing Chinese Medicine Syndrome Element of Blood Stasis Presented a Better Performance Compared to APRI and FIB-4 in Diagnosing Advanced Fibrosis in Patients with Chronic Hepatitis B

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This study aims to explore a useful noninvasive assessment containing TCM syndrome elements for liver fibrosis in CHB patients. The demographic, clinical, and pathological data were retrospectively collected from 709 CHB patients who had ALT less than 2 times the upper limit of normal from April 2009 to October 2012. Logistical regression and area under receiver-operator curve (AUROC) were used to determine the diagnostic performances of simple tests for advanced fibrosis (Scheuer stage, F ≥ 3). Results showed that the most common TCM syndrome element observed in this CHB population was dampness and Qi stagnation, followed by blood stasis, by heat, and less by Qi deficiency and Yin deficiency. The logistical regression analysis identified AST ≥ 35 IU/L, PLT ≤ 161 × 10^9/L, and TCM syndrome element of blood stasis as the independent risk factors for advanced fibrosis. Therefore, a score model containing these three factors was established and tested. The score model containing blood stasis resulted in a higher AUC (AUC = 0.936) compared with APRI (AUC = 0.731) and FIB-4 (AUC = 0.709). The study suggested that the score model containing TCM syndrome element of blood stasis could be used as a useful diagnostic tool for advanced fibrosis in CHB patients and presented a better performance compared to APRI and FIB-4.

1. Background

Hepatitis B virus (HBV) carriers and chronic hepatitis B (CHB) patients with minimally elevated alanine aminotransf erase (ALT) have been increasingly attended in recent years. More and more evidences showed that patients with ALT less than 2 times the upper limit of normal (<2ULN) could still eventually develop clinical complications [1]. Several studies [2, 3] observed significant fibrosis in CHB patients with minimally elevated ALT, even in patients with normal ALT. It is well known that advanced liver fibrosis results in cirrhosis, liver failure, and portal hypertension and often requires liver transplantation. So, it is quite important to identify the patients with higher risk of developing advanced fibrosis and then to diagnose and intervene early. As the “gold standard” to diagnose and determine the stages of fibrosis in CHB patients, however, the wide application of liver biopsy was limited due to its invasive pattern, risks, and expensive cost. The available noninvasive diagnostic assessments including APRI, FIB-4, and FibroTest were also less optimal, although they have been increasingly accepted in clinical practice. Based on our clinical experiences in diagnosis and treatment with Traditional Chinese Medicine (TCM) in CHB patients with fibrosis, TCM syndrome elements would improve the diagnosis performance when combined with the markers with confirmed diagnostic effects in these patients.

In a word, previous studies in domain of modern medicine have identified several useful markers in predicting liver fibrosis in CHB patients [2, 4–6]; however, there were few studies that evaluated the TCM factors in predicting and diagnosing liver fibrosis in CHB patients with ALT < 2ULN in the domain of TCM sciences. So, we conducted this study in CHB patients with ALT < 2ULN to identify the characteristics of TCM syndromes associated with the developing of liver
fibrosis and to explore a useful noninvasive assessment that contained the TCM syndrome elements for diagnosing liver fibrosis in CHB patients.

2. Methods

2.1. Subjects. As an earlier stage of a study registered in 2014 evaluating the blocking effects of liver fibrosis with TCM treatment in CHB patients with ALT < 2ULN, the demographic, clinical, and pathological data were retrospectively collected from CHB patients who had ALT < 2ULN and performed liver biopsy in the Guangdong Provincial Hospital of Chinese Medicine between April 2009 and October 2012. The diagnoses of CHB and live fibrosis were determined according to the criteria described in Guideline of Prevention and Treatment for Chronic Hepatitis B (2010 version) [7] and Guideline for Diagnostic and Treatment of Hepatic Fibrosis [8], and the TCM syndrome elements were determined according to Standards of Traditional Chinese Medicine syndrome differentiation for viral hepatitis (trial implementation) [9] and the diagnostic standard of TCM syndrome elements for CHB patients [10].

All patients who meet the following inclusion criteria could be enrolled: (1) those aged from 18 to 65 years, (2) those having a diagnosis of CHB, (3) HBsAg being positive and ALT being less than 2ULN for at least 6 months prior to the study, and (4) patients with diagnosis of single or combined TCM syndrome (e.g., dampness or heat or blood stasis). Patients with any of the following conditions were excluded from the study: (1) coinfection with another hepatitis virus or human immunodeficiency virus; (2) concomitant liver and gallbladder diseases which can interfere in the evaluation of risk factors including evident advanced primary biliary cirrhosis, autoimmune hepatitis, decompensated cirrhosis, severe hepatitis, or hepatic carcinoma and a history of excessive alcohol consumption (20 g per day for female and 30 g per day for male); (3) concomitant uncontrolled serious heart, kidney, lung, endocrine, blood, metabolic, or gastrointestinal primary disease or mental illness; (4) patients who received any antifibrotic treatments within 6 months prior to the enrollment. The study has been approved by the ethics committee of Guangdong Provincial Hospital of Chinese Medicine, and written informed consent was obtained from all patients during outpatient follow-up or by telephone and letter follow-up before this study.

2.2. Clinical and Laboratory Assessment. The demographic, clinical, and laboratory data were collected at the time of liver biopsy, including age, gender, levels of ALT, aspartate aminotransferase (AST), g-glutamyl transpeptidase (GGT), albumin, platelet count, and viral parameters. Serum HBsAg was measured by electrochemical immunoassay (Elecsys 2010; Roche Diagnostics, Mannheim, Germany). Serum HBV DNA was measured with a lower limit of detection of 500 IU/mL (ABI 7300, Applied Biosystems Inc., USA).

2.3. Histological Assessment. Liver biopsy was performed using 16G MAXCO needles (Bard Co., Murray Hill, NJ, USA).

The specimens were fixed in 10% formalin, paraffin-embedded, and stained with hematoxylin and eosin in turn. A minimum of 15 mm length of liver tissue and at least five portal tracts were required for diagnosis. Fibrosis stage was determined according to Scheuer’s classification: F0, no fibrosis; F1, enlarged fibrotic portal tracts; F2, periportal or portal-portal septa, but intact architecture; F3, fibrosis with architectural distortion, but no obvious cirrhosis; and F4, cirrhosis. Liver fibrosis beyond the portal tract (stage F3 or F4) was considered advanced fibrosis [11].

2.4. Data Analysis. Continuous variables were expressed as mean ± standard deviation, or median and interquartile range, and were compared with Student t-test or nonparameter test (Mann-Whitney) as appropriate. Zero and one were used to express binary enumeration data and frequency was counted (such as the measurement of TCM variables). Categorical parameters among groups were compared by chi-squared test. Univariate analysis was performed to identify the variables associated with advanced fibrosis. Then, a multivariate logistic regression analysis that contained these significant variables (P < 0.05) identified by univariate analysis was performed to determine the risk factors for advanced fibrosis. Area under receiver-operator curve (AUROC) was used to calculate the diagnostic accuracy of the score model established in this study as well as aspartate aminotransferase to platelet ratio index (APRI) and fibrosis index based on the 4 factors (FIB-4) in diagnosing advanced fibrosis. Delong’s test was used to compare the AUC of these three noninvasive tests. Statistical significance was taken as P < 0.05 at two sides. All statistical analysis was performed using SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA).

3. Results and Discussion

3.1. Results

3.1.1. Characteristics of the 709 CHB Patients with ALT < 2ULN. The basic demographic and clinical characteristics of the 709 enrolled CHB patients were showed in Table 1. Among the 709 patients, 436 (61.49%) were patients with normal ALT and 273 (38.51%) were patients with minimally elevated ALT (40 < ALT < 80); 109 (15.4%) patients had advanced inflammation activity and 232 (32.7%) patients had advanced fibrosis. The demographic data showed that there were more men than women and the median age was 39 years in all patients. The patients in minimally elevated ALT group had significantly higher levels of ALT, AST, and GGT, serum level of HBV DNA, grade of inflammation activity, and the percentage of HBeAg (+) patients than patients in normal ALT group (all of P < 0.001, except P = 0.018 for inflammation activity). However, no significant difference was found on the stage of fibrosis between these two groups (P > 0.05).

3.1.2. Features of TCM Syndrome Elements Distribution in 709 CHB Patients with ALT < 2ULN. As shown in Table 2, among the TCM syndrome elements of CHB patients, dampness
and Qi stagnation had the highest frequency, followed by blood stasis, by heat, and less by Qi deficiency and Yin deficiency. Almost all patients had a combined syndrome, and only 29 (4.09%) patients had single syndrome in these 709 CHB patients with ALT < 2ULN.

### 3.1.3. Univariate and Multivariate Analysis of Factors Associated with Advanced Fibrosis

Compared with the patients without advanced fibrosis \((n = 477)\), CHB patients with advanced fibrosis \((n = 232)\) had a significant higher percentage of male patients \((73.7\% \text{ versus } 66.0\%, \text{P} = 0.039)\) and higher levels of age \((42.2 \text{ versus } 37.9 \text{ years, } \text{P} \leq 0.001)\), AST \((34.3 \text{ versus } 27.9 \text{ IU/L, } \text{P} < 0.001)\), and GGT \((47.4 \text{ versus } 27.3 \text{ IU/L, } \text{P} < 0.001)\) but lower platelet counts \((161.7 \text{ versus } 203.7 \times 10^9 / \text{L, } \text{P} < 0.001)\) and HBV DNA \((5.08 \text{ versus } 5.55 \log_{10} \text{ IU/mL})\). Moreover, all the CHB patients with advanced fibrosis showed higher frequency of the TCM syndrome elements of blood stasis and Qi deficiency \((\text{P} < 0.001)\) (Table 3) and lower frequency of the TCM syndrome element of heat.

The univariate analysis identified the variables including male, age, AST, PLT, GGT, HBV DNA, and TCM syndrome elements of blood stasis, Qi deficiency, and heat as the factors associated with advanced fibrosis. However, further multivariate logistic regression analysis including all above factors revealed that only increased serum AST level, decreased PLT count, and TCM syndrome element of blood stasis were associated with advanced fibrosis. Based on the measurements of mean level of AST and PLT in patients with advanced fibrosis, we selected AST \(\geq 35 \text{ IU/L, PLT } \leq 161 \times 10^9 / \text{L, and TCM syndrome element of blood stasis as the independent factors for advanced fibrosis with regression coefficients of 0.816, 1.379, and 5.457, respectively (Table 4). Then as shown in Table 5, each factor was assigned a score based on regression coefficients to establish a simplified score model to serve as a noninvasive assessment for diagnosing advanced fibrosis.

### 3.1.4. Comparison of Diagnostic Accuracy of the Score Model Containing Blood Stasis, APRI, and FIB-4 in Advanced Fibrosis

As shown in Figure 1, the score model containing blood stasis resulted in a higher AUC \((\text{AUC} = 0.936)\) compared with APRI \((\text{AUC} = 0.731)\) and FIB-4 \((\text{AUC} = 0.709)\) and showed a statistically better performance than APRI and FIB-4 (both \(P < 0.05\)). Moreover, at the cutoff point of 2 determined by ROC analysis, sensitivity and specificity of the score model established in our study were 98.3% and 80.0%, and positive predictive value and negative predictive value were 71.5% and 98.9%, respectively, at the maximum Youden index when used to diagnose advanced fibrosis. A score of 0-1 indicated patients at lower risk of advanced fibrosis \((0–1.1\%)\), whereas a score of 2–4 indicated patients at higher risk \((71.5–96.4\%)\).

### 3.2. Discussion

In CHB patients, liver biopsy is currently used as the “gold standard” to diagnose and determine the stages of fibrosis. However, its wide application was limited due to its invasive pattern, risks, and expensive cost. Therefore, there is a great need of some noninvasive assessments which can more accurately identify patients with advanced fibrosis. The available noninvasive assessments including APRI, FIB-4, and FibroTest have gained increasing acceptance in clinical practice [12]. However, there are still some

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**Table 1: Characteristics of 709 CHB patients with ALT < 2ULN.**

| Variables                      | All patients \((n = 709)\) | 0 < ALT \(\leq 40\) \((n = 436)\) | 40 < ALT \(\leq 80\) \((n = 273)\) | \(P\) value |
|-------------------------------|-----------------------------|-----------------------------------|-----------------------------------|-------------|
| **Demographic characteristics** |                             |                                   |                                   |             |
| Age (years, median (IQR))     | 39.0 (31.5–46.0)            | 39.0 (32.0–45.0)                  | 38.0 (31.0–47.0)                 | 0.823       |
| Males, n (%)                  | 486 (68.5%)                 | 273 (62.6%)                       | 213 (78%)                        | <0.001      |
| **Laboratory data**           |                             |                                   |                                   |             |
| ALT (IU/L, median (IQR))      | 35.0 (22.0–47.0)            | 25.0 (18.0–33.0)                  | 51.0 (45.0–64.0)                 | <0.001      |
| AST (IU/L, median (IQR))      | 26.0 (21.0–36.0)            | 22.6 (19.0–27.0)                  | 36.0 (30.0–43.0)                 | <0.001      |
| ALB (g/L, median (IQR))       | 44.1 (42.0–46.4)            | 43.9 (42.0–46.1)                  | 44.4 (41.95–46.85)               | 0.280       |
| GGT (IU/L, median (IQR))      | 24.0 (17.5–38.0)            | 21.0 (15.0–33.0)                  | 31.0 (22.0–45.0)                 | <0.001      |
| PLT (10^9/L, median (IQR))    | 186 (152.0–224.0)           | 187 (151.0–223.0)                 | 185 (152.0–225.0)                | 0.828       |
| HBsAg (+), n (%)              | 331 (46.7%)                 | 178 (40.8%)                       | 153 (56.0%)                      | <0.001      |
| HBV DNA (log_{10} IU/mL), median (IQR) | 5.49 (3.62–7.21)          | 4.72 (3.24–6.79)                  | 6.29 (4.98–7.59)                 | <0.001      |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; GGT, g-glutamyl transpeptidase; PLT, platelet; HBsAg: hepatitis B e antigen; IQR, interquartile range.
Table 2: Distribution of TCM syndrome elements in CHB patients with ALT < 2ULN.

| TCM syndrome elements | Dampness | Qi stagnation | Blood stasis | Heat | Qi deficiency | Yin deficiency |
|-----------------------|----------|----------------|--------------|------|---------------|---------------|
| N                     | 697      | 651            | 311          | 304  | 173           | 7             |
| %                     | 98.3%    | 91.8%          | 43.9%        | 42.9%| 24.4%         | 1.0%          |

TCM, Traditional Chinese Medicine; CHB, chronic hepatitis B.

Table 3: Comparison between the patients with advanced fibrosis and without advanced fibrosis.

| Variables                | Patients without advanced fibrosis (n = 477) | Patients with advanced fibrosis (n = 232) | P value |
|--------------------------|---------------------------------------------|------------------------------------------|---------|
| Demographic characteristics |                                            |                                          |         |
| Age (years) (X ± SD)     | 37.9 ± 9.7                                  | 42.2 ± 10.6                              | <0.001  |
| Males, n (%)             | 315 (66.0%)                                 | 171 (73.7%)                              | 0.039   |
| Laboratory data          |                                            |                                          |         |
| ALT (IU/L) (X ± SD)      | 35.9 ± 17.8                                 | 37.7 ± 16.9                              | 0.205   |
| AST (IU/L) (X ± SD)      | 27.9 ± 11.9                                 | 34.3 ± 17.9                              | <0.001  |
| ALB (g/L) (X ± SD)       | 44.4 ± 3.9                                  | 44.6 ± 26.1                              | 0.819   |
| GGT (IU/L) (X ± SD)      | 27.3 ± 19.8                                 | 47.4 ± 55.9                              | <0.001  |
| PLT (10^9/L) (X ± SD)    | 203.7 ± 53.2                                | 161.7 ± 50.0                             | <0.001  |
| HBeAg (+) patients, n (%)| 238 (49.9%)                                 | 93 (40.1%)                               | 0.014   |
| HBV DNA (log_{10} IU/mL, X ± SD) | 5.55 ± 2.09                                  | 5.08 ± 1.75                              | 0.004   |

| TCM syndrome elements    |                                            |                                          |         |
| Dampness                | 471 (98.7%)                                 | 226 (97.4%)                              | 0.198   |
| Qi stagnation           | 438 (91.8%)                                 | 213 (91.8%)                              | 0.780   |
| Blood stasis            | 84 (17.6%)                                  | 227 (97.8%)                              | <0.001  |
| Heat                    | 269 (56.4%)                                 | 35 (15.1%)                               | <0.001  |
| Qi deficiency            | 101 (21.2%)                                 | 72 (31.0%)                               | 0.004   |
| Yin deficiency           | 4 (0.8%)                                    | 3 (1.3%)                                 | 0.566   |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; GGT, g-glutamyl transpeptidase; PLT, platelet; HBeAg, hepatitis B e antigen; TCM, Traditional Chinese Medicine.

In addition to the TCM syndrome element of blood stasis, the multivariate analysis also identified the markers of AST ≥ 35 IU/L, PLT ≤ 161 x 10^9/L as the independent risk factors for advanced fibrosis. As planned, a risk score model based on the detected factors was established. The score model containing above three risk factors resulted in a higher AUC (AUC = 0.936), compared with APRI (AUC = 0.731) and FIB-4 (AUC = 0.709). The more important thing was that our score model had high sensitivity and specificity of 98.3% and 80.0%, respectively. It suggested that our score model might become a more useful noninvasive assessment for advanced fibrosis compared to APRI and FIB-4. However, a potential limitation of this study was that it was a retrospective, single-center study: Stratification of continuous variables as well as conversion of the regression coefficients to score values although necessary for clinical practicality could be assumed.
Table 4: The variables associated with advanced fibrosis identified by multivariate logistic regression.

| Variables                                      | Regression coefficient | SE   | Wald | OR   | P value |
|------------------------------------------------|------------------------|------|------|------|---------|
| AST ≥ 35 IU/L                                  | 0.816                  | 0.317| 6.65 | 2.26 | 0.010   |
| PLT ≤ 161 × 10^9/L                             | 1.379                  | 0.295| 21.92| 3.97 | <0.001  |
| With TCM syndrome element of blood stasis      | 5.457                  | 0.480| 129.3| 234.4| <0.001  |

AST, aspartate aminotransferase; PLT, platelet; TCM, Traditional Chinese Medicine.

Table 5: Regression coefficients and the assigned score of factors associated with advanced fibrosis.

| Risk factors                                      | Regression coefficient | P value | Risk score |
|---------------------------------------------------|------------------------|---------|------------|
| AST ≥ 35 IU/L                                     | 0.816                  | 0.010   | 1          |
| PLT ≤ 161 × 10^9/L                               | 1.379                  | <0.001  | 1          |
| TCM syndrome element of blood stasis              | 5.457                  | <0.001  | 2          |

AST, aspartate aminotransferase; PLT, platelet; TCM, Traditional Chinese Medicine.

4. Conclusions

This study clearly demonstrated that the pathogenic factors of CHB patients were mainly dampness, Qi stagnation, heat, and blood stasis. Moreover, the score model containing TCM syndrome of blood stasis, serum ALT, and PLT could be used as a useful noninvasive assessment for advanced fibrosis. However, the diagnostic and predicting role of our noninvasive assessment containing TCM syndrome element of blood stasis for advanced fibrosis will be confirmed in prospective study in the future.

Abbreviations

CHB: Chronic hepatitis B  
TCM: Traditional Chinese Medicine  
HBV: Hepatitis B virus  
ALT: Alanine aminotransferase  
<2ULN: Not more than 2 times the upper limit of normal  
AST: Aspartate aminotransferase  
GGT: g-glutamyl transpeptidase  
PLT: Platelet  
ALB: Albumin  
GLB: Globulin  
HBeAg: Hepatitis B e antigen  
APRI: AST to platelet ratio index  
FIB-4: Fibrosis index based on the 4 factors.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors’ Contribution

Xiao-Ling Chi conceived and designed the clinical trial, recruited patients, and wrote and gave final approval for the paper. Mei-Jie Shi, Huan-Ming Xiao, and Yu-Bao Xie recruited patients, performed the clinical trial, contributed reagents and materials, and gave final approval for the paper. Gao-Shu Cai recruited patients and gave final approval for the paper. All authors read and approved the final paper.

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References

[1] M.-F. Yuen, H.-J. Yuan, D. K.-H. Wong et al., "Prognostic determinants for chronic hepatitis B in Asians: therapeutic implications," *Gut*, vol. 54, no. 11, pp. 1610–1614, 2005.

[2] S. Alam, N. Ahmad, G. Mustafa, A. Shrestha, A. K. M. K. Alam, and M. Khan, "Evaluation of normal or minimally elevated alanine transaminase, age and DNA level in predicting liver histological changes in chronic hepatitis B," *Liver International*, vol. 31, no. 6, pp. 92–94, 2013.

[3] Y.-H. Huang, Z.-J. Yu, C. Wang, B. Zhou, and J.-L. Hou, "Relationship between hepatitis B virus genotypes and liver fibrosis," *Nan Fang Yi Ke Da Xue Xue Bao*, vol. 27, no. 7, pp. 1012–1014, 2007.

[4] Y. Wang, M.-Y. Xu, R.-D. Zheng et al., "Prediction of significant fibrosis and cirrhosis in hepatitis B e-antigen negative patients with chronic hepatitis B using routine parameters," *Hepatology Research*, vol. 43, no. 5, pp. 441–451, 2013.

[5] Chinese Society of Hepatology and Chinese Society of Infectious Diseases. Chinese Medical Association, “The guideline of prevention and treatment for chronic hepatitis B (2010 version),” Chinese Journal of Hepatology, vol. 32, no. 4, pp. 405–415, 2011.

[6] Liver Disease Committee. Chinese Association of Integrative Medicine, “Guidelines for the diagnosis and treatment of liver fibrosis in integrative medicine practice,” *Chinese Journal of Hepatology*, vol. 14, no. 11, pp. 866–870, 2006.

[7] Professional Committee of Liver Diseases of China Association of Chinese Medicine, “Standards of traditional Chinese medicine syndrome differentiation for viral hepatitis (trial implementation),” Zhong Yi Za Zhi, vol. 33, no. 11, pp. 1437–1445, 2015.

[8] Chinese Society of Hepatology and Chinese Society of Infectious Diseases. Chinese Medical Association, “The guideline of prevention and treatment for chronic hepatitis B (2010 version),” *Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi*, vol. 27, no. 2, pp. 1437–1445, 2015.

[9] M.-D. Zeng, L.-G. Lu, Y.-M. Mao et al., "Prediction of significant fibrosis in HBeAg-positive patients with chronic hepatitis B by a non invasive model," *Hepatology Research*, vol. 42, no. 6, pp. 1437–1445, 2005.

[10] X. Hu, Z. Liu, and J. Sun, "Explanation of the ‘guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection 2015’: non-invasive assessment of liver fibrosis, treatment strategy and implementation of national programs," *Journal of Clinical Hepatology*, vol. 31, no. 6, pp. 829–832, 2015.

[11] H.-P. Xie, H.-Z. Yang, W.-K. Wu et al., “Chinese medicine syndrome distribution of chronic hepatitis B virus carriers in immunotolerant phase,” *Chinese Journal of Integrative Medicine*, vol. 20, no. 2, pp. 94–100, 2014.

[12] Z. M. Tang, Q. J. Ru, and Z. E. Zhang, “Clinical study on relationship between liver-blood stasis and liver fibrosis,” *Zhongguo Zhong Xi Yi Jie He Za Zhi*, vol. 17, no. 2, pp. 81–83, 1997.

[13] S. Y. Liu, Y. Q. Zhang, Y. L. Liu, P. Guo, and C. M. Zhou, “Intervention of chronic hepatitis B liver fibrosis patients in different stages by syndrome typing and different activating blood removing stasis methods: a clinical study,” *Zhongguo Zhong Xi Yi Jie He Za Zhi*, vol. 33, no. 11, pp. 1457–1461, 2013.