

Original Article

Serum CHI3L1 as a diagnostic marker and risk factor for liver fibrosis in HBeAg-negative chronic hepatitis B

Yuecui Li, Chenghang Li*, Lili Zhang*, Weiyue Hu, Hongxia Luo, Jin Li, Shuai Qiu, Shengwei Zhu

Department of Infection Diseases, The First People's Hospital of Yongkang, Yongkang 321300, Zhejiang, China.

*Equal contributors.

Received March 9, 2022; Accepted May 16, 2022; Epub June 15, 2022; Published June 30, 2022

Abstract: Chronic hepatitis B (CHB) as the major inducement of hepatocellular carcinoma and cirrhosis, imposes a heavy health burden upon patients. This research aims to investigate the diagnostic value of serum chitinase 3-like 1 (CHI3L1) in hepatitis B e antigen (HBeAg)-negative CHB liver fibrosis (LF) and to analyze the risk factors. We selected 78 patients with HBeAg-negative CHB admitted to our hospital between October 2018 and October 2019, and grouped them ($F_{0,1}$ group, n=38; $F_{2,4}$ group, n=40) based on their stages evaluated by the METAVIR scoring system. Cubital venous blood was collected from patients in both groups to quantify the content of CHI3L1 after serum extraction. The correlation of CHI3L1 in CHB with LF diagnostic markers fibrosis 4 (FIB-4) and γ -glutamyltranspeptidase (GGT) to platelet (PLT) ratio (GPR) as well as LF staging was analyzed. The diagnostic value of serum CHI3L1 in HBeAg-negative CHB fibrosis staging was analyzed by receiver operating characteristic (ROC) curve, and the multivariate analysis of the risk factors for FB in HBeAg-negative CHB patients was performed using the Logistic regression model. This study found that serum CHI3L1 was positively correlated not only with LF markers (FIB-4, GPR), but also with LF staging. Serum CHI3L1 had high diagnostic efficiency for LF staging, with the sensitivity and specificity of 80.00% and 71.05%, respectively. In addition, CHI3L1, FIB-4, and GPR were identified to be the risk factors for LF in HBeAg-negative CHB. In conclusion, serum CHI3L1 can be used as a diagnostic marker and risk factor for LF in patients with HBeAg-negative CHB.

Keywords: CHI3L1, HBeAg, chronic hepatitis B, liver fibrosis, diagnosis

Introduction

Chronic hepatitis B (CHB) is a high-risk viral infectious disease with poor prognosis, and its etiology is related to HBV infection [1]. According to epidemiological statistics, there are approximately 400 million patients infected with HBV worldwide and about 1 million annual deaths due to the disease [2]. The typical characteristic of HBV infection is the secretion of hepatitis B surface antigen (HBsAg) by the infected hepatocytes [3]. Furthermore, the infection process is influenced by hepatitis B e antigen (HBeAg), the presence of which can drive HBV replication, but most patients with CHB are HBeAg-negative [4, 5]. Liver fibrosis (LF) in these patients leads to elevated risk of cirrhosis, and in severe cases, LF and cirrhosis can increase the risk of primary liver cancer and death [6]. The pathological process of LF is reversible. Early diagnosis and timely effective

tive treatment are conducive to improving the prognosis of patients and delaying or avoiding the transition to cirrhosis [7]. Therefore, finding effective diagnostic indicators and risk factors for LF in HBeAg-negative CHB is of great significance for improving patient outcomes and reducing mortality.

Chitinase 3-like 1 (CHI3L1), or YKL-40, is a member of the mammalian chitinase family, can be secreted by fibroblast-like cells, hepatic stellate cells and cancer cells, etc. [8]. It mediates a wide range of biological processes and participates in regulating biological processes such as tissue repair, pathogen defense and macrophage differentiation [9]. It is also a fibroblast growth factor and is related to LF in patients with chronic liver diseases [10]. CHI3L1 is highly and specifically expressed in liver tissue and can function as a serum index to evaluate the degree of LF [11]. Huang et al. [12]

The role of CHI3L1 in chronic hepatitis B liver fibrosis

reported that CHI3L1 can be used in the diagnosis of CHB LF as a noninvasive diagnostic model in combination with conventional clinical indicators. According to Jin et al. [13], CHI3L1 is a feasible new serum index used to monitor LF progression in CHB. Fibrosis 4 (FIB-4) and γ -glutamyl transpeptidase (GGT) to platelet (PLT) ratio (GPR) are both non-invasive serum markers of CHB fibrosis and can be used as surrogate markers for liver biopsy [14]. CHI3L1, FIB-4, and GGT are all closely associated with LF, both in chronic hepatitis C and in CHB, but their correlations in HBeAg-negative CHB patients remain to be clarified [15, 16].

Currently, the diagnostic value of CHI3L1 in LF of HBeAg-negative CHB patients is not clear. Accordingly, this study mainly analyzed the diagnostic value of CHI3L1 as a serum index in HBeAg-negative CHB patients with LF and the risk factors, aiming at rendering novel references for the diagnosis of such patients.

Materials and methods

General data

A total of 78 patients with HBeAg-negative CHB (male-to-female ratio: 47:31) admitted consecutively to The First People's Hospital of Yongkang, Yongkang between October 2018 and October 2019 were enrolled. Inclusion criteria: confirmed diagnosis of CHB (persistent serum HBsAg for more than six months), liver biopsies performed within one week after blood laboratory tests, HBeAg-negative, age: 16-80 years old, complete clinical medical records, high compliance, normal cognitive and communication skills, and no medication taken within the past six months that may affect the experimental results. Exclusion criteria: other types of hepatitis virus infection, malignant tumor(s), other liver diseases, insufficient liver biopsy samples (<1.5 cm), other serious organic diseases, lactation or pregnancy. This study has been approved by the Ethics Committee of the First People's Hospital of Yongkang. All subjects were informed and signed informed consent.

Histological analysis and grouping

Ultrasound guided liver biopsy was performed using a 16 G needle. Liver samples with a minimum length of 1.5 cm and at least 7 intact

portal vein bundles were fixed with 10% formalin and embedded in paraffin. Histological analysis was performed by hematoxylin and eosin, Masson's trichrome and reticulin staining. By referring to the METAVIR scoring system [17], patients were pathologically analyzed and grouped ($F_{0,1}$, n=38; F_{2-4} , n=40), among which the $F_{0,1}$ group was non-significant hepatic fibrosis group, and the F_{2-4} group was significant hepatic fibrosis group. LF staging: FO = no fibrosis, F1 = portal vein fibrosis without septa, F2 = portal vein fibrosis with rare septa, F3 = large septa without cirrhosis, F4 = cirrhosis.

Measurement indicators

Fasting serum samples were collected one week after liver biopsy to measure serum CHI3L1 levels using the ELISA kit (CUSABIO Technology LLC, Wuhan, China, CSB-E136-08H).

Other detection indexes: Hepatitis B virus (HBV) DNA was detected by real-time PCR system (Xi'an Tianlong Science and Technology Co., Ltd., Xi'an, China, Gentier 96E). The contents of PLT, hemoglobins (Hb), neutrophils (N), lymphocytes (LY), and monocytes (MNC) were measured using an automatic hematology analyzer (Shanghai Jmmedical Instrument Co., Ltd., Shanghai, China, B3513). The levels of serum biochemical indexes such as total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ -GGT were determined by an automatic biochemical analyzer (Nanjing Vedeng Medical Co., Ltd., Nanjing, China, V503801).

Fib-4 and GPR are calculated as follows: $FIB-4 = (\text{Age} [\text{years}] \times \text{AST} [\text{U/L}]) / (\text{PLT} [10^9/\text{L}] \times \text{ALT} [\text{U/L}]^{1/2})$; $GPR = (\text{GGT} / \text{upper limit of normal}) \times 100 / \text{PLT}$.

Statistical analysis

SPSS 22.0 (Beijing EasyBio Technology Co., Ltd., China) was used for statistical analysis. The Chi-square test was used for inter-group comparisons of counting data, expressed as number of cases/percentage (n/%). When the theoretical frequency in the Chi-square test was <5, a continuous correction chi-square test was applied. As to measurement data recorded as mean \pm SEM, inter-group comparisons were performed by the independent sam-

The role of CHI3L1 in chronic hepatitis B liver fibrosis

Table 1. Analysis of pathological parameters of HBeAg-negative CHB liver fibrosis [n (%), Mean \pm SD]

Factors	n	F _{0,1} group (n=38)	F _{2,4} group (n=40)	χ^2/t	P
Sex				0.947	0.330
Male	47	25 (65.79)	22 (55.00)		
Female	31	13 (34.21)	18 (45.00)		
Age (years)	78	37.89 \pm 11.09	41.73 \pm 11.55	1.496	0.139
BMI (kg/m ²)	78	28.26 \pm 4.66	28.96 \pm 6.91	0.522	0.603
HBV DNA log ₁₀ (IU/mL)	78	5.06 \pm 1.04	5.24 \pm 1.15	0.724	0.471
PLT (10 ⁹ /L)	78	186.28 \pm 33.28	182.74 \pm 20.20	0.571	0.570
Hemoglobins (%)	78	13.73 \pm 1.32	14.06 \pm 1.39	1.074	0.286
Neutrophils (%)	78	58.22 \pm 7.09	61.32 \pm 8.12	1.792	0.077
Lymphocytes (%)	78	33.84 \pm 5.75	31.48 \pm 7.00	1.622	0.109
Monocytes (%)	78	4.60 \pm 2.29	4.84 \pm 2.57	0.435	0.665
TBIL (μ mol/L)	78	18.34 \pm 7.07	19.23 \pm 8.95	0.486	0.629
ALT (U/L)	78	46.14 \pm 19.38	51.82 \pm 28.81	1.016	0.313
AST (U/L)	78	46.64 \pm 19.43	42.50 \pm 26.00	0.793	0.430
FIB-4	78	290.99 \pm 105.26	392.29 \pm 89.59	4.585	<0.001
GPR	78	0.56 \pm 0.27	0.70 \pm 0.24	2.423	0.018
CHI3L1 (ng/mL)	78	105.50 \pm 42.55	133.43 \pm 26.96	3.481	<0.001

Note: HBeAg, hepatitis B e antigen; CHB, Chronic hepatitis B; BMI, Body Mass Index; HBV, Hepatitis B Virus; PLT, Platelet; TBIL, total bilirubin; ALT, alanine transaminase; AST, aspartate transaminase; FIB-4, Fibrosis-4; GPR, gamma-glutamyl transpeptidase to platelet ratio; CHI3L1, Chitinase 3-like 1.

ples t-test. The efficacy of CHI3L1 in differentiating LF was analyzed using receiver operating characteristic (ROC) curves. Correlations of CHI3L1 with LF markers and LF staging were discussed using Pearson's coefficients and Spearman correlation coefficients, respectively. Risk factors for LF in HBeAg-negative CHB were analyzed by logistics multifactor regression analysis. The significance level was $P < 0.05$.

Results

Pathological parameters analysis of LF in HBeAg-negative CHB

The statistical results of patients' pathological data showed that there were no statistical differences in sex, age, body mass index (BMI), HBV DNA, PLT, Hb, N, LY, MNC, TBIL, ALT and AST between the groups ($P > 0.05$), while there were statistical differences in FIB-4, GPR and CHI3L1 ($P < 0.05$, **Table 1**).

Correlation of serum CHI3L1 level with LF markers and staging

Serum CHI3L1 had a significant positive correlation with LF markers FIB-4 and GPR ($r = 0.433$,

$P < 0.01$; $r = 0.409$, $P < 0.01$), as indicated by Pearson correlation coefficients. The relationship between serum CHI3L1 level and LF staging was analyzed by Spearman correlation coefficients. We defined F_{0,1} group as 1 and F_{2,4} group as 2. The data showed a significant positive correlation between serum CHI3L1 and LF staging ($r = 0.523$, $P < 0.01$). See **Figure 1**.

Diagnostic significance of serum CHI3L1 in HBeAg-negative CHB LF staging

Through ROC curve analysis, it was found that the area under the curve (AUC) of serum CHI3L1 in diagnosing LF staging was 0.818, the optimal cut-off was 118.2 ng/mL, the sensitivity was 80.00%, and the specificity was 71.05%. See **Figure 2**.

Analysis of risk factors of LF in HBeAg-negative CHB

FIB-4, GPR and CHI3L1 with significant differences were included in the analysis and assigned as dependent variables. Taking whether it affects HBeAg-negative CHB LF as the dependent variable, multivariate analysis was performed using the Logistic regression model.

The role of CHI3L1 in chronic hepatitis B liver fibrosis

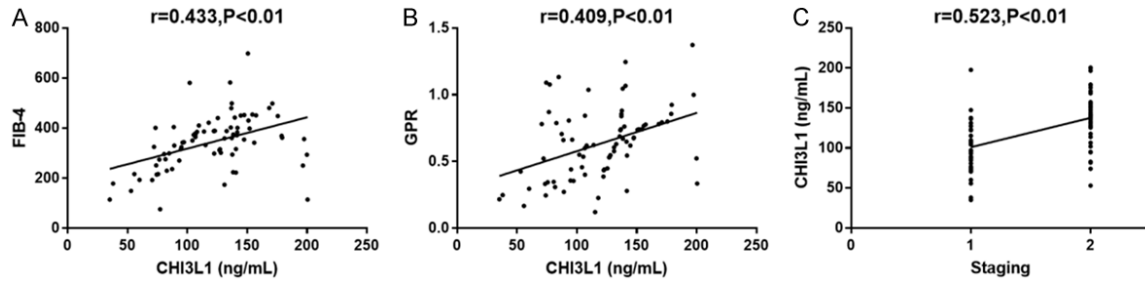


Figure 1. Correlations of serum CHI3L1 level with liver fibrosis markers and staging. A. Relationship between serum CHI3L1 level and FIB-4. B. Relationship between serum CHI3L1 level and GPR. C. Relationship between serum CHI3L1 level and liver fibrosis staging. Note: FIB-4, Fibrosis-4; GPR, gamma-glutamyl transpeptidase to platelet ratio; CHI3L1, Chitinase 3-like 1.

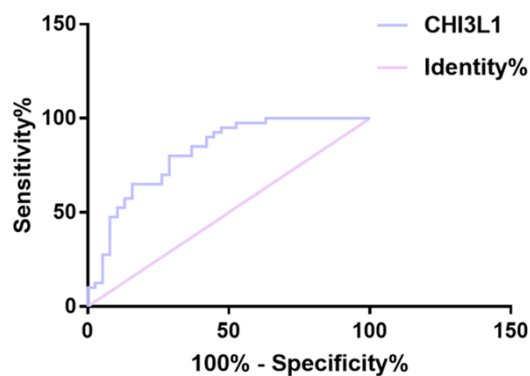


Figure 2. Diagnostic value of serum CHI3L1 in HBeAg-negative CHB liver fibrosis staging. Note: CHI3L1, Chitinase 3-like 1; HBeAg, hepatitis B e antigen; CHB, Chronic hepatitis B.

Table 2. Logistic multivariate regression analysis assignment

Factors	Variables	Assignment
FIB-4	X1	Continuous variable
GPR	X2	Continuous variable
CHI3L1	X3	Continuous variable

Note: FIB-4, Fibrosis-4; GPR, gamma-glutamyl transpeptidase to platelet ratio; CHI3L1, Chitinase 3-like 1.

The results revealed that FIB-4 ($P=0.040$), GPR ($P=0.022$) and CHI3L1 ($P<0.001$) were independent risk factors for LF in HBeAg-negative CHB patients. See **Tables 2, 3**.

Discussion

LF is involved in the pathological process of CHB, which is also an intermediate step in the transition to cirrhosis [18]. Severe LF in CHB patients can lead to an increased risk of complications, so the prediction of LF staging

is crucial for optimizing CHB treatment [19]. Liver biopsy is currently the gold standard for the differentiation of LF, but this method is not ideal because of its invasiveness, sampling errors and limitations [20]. Serum diagnostic markers, on the other hand, are increasingly popular in virtue of their non-invasiveness, simple sampling and low cost [21]. Therefore, finding effective serum markers is of great significance for diagnosing LF in CHB patients.

CHI3L1 is a chitinase-like soluble protein that has no chitinase activity [8]. It has been found to be abnormally upregulated in serum in a variety of liver diseases, including LF, nonalcoholic fatty liver disease, alcoholic liver disease and hepatocellular carcinoma, suggesting its specific expression in liver diseases [22]. Studies on the underlying mechanism have indicated that inhibiting CHI3L1 has beneficial effects on the improvement of various liver diseases. For example, down-regulation of CHI3L1 has been found to inhibit the activation and proliferation of T cells in mesenchymal stem cells and effectively improve concanavalin A (Con A)-induced liver injury [23]. In a mouse model of nonalcoholic fatty liver disease, the liver insulin signal transmission of mice was significantly improved, and the lipid accumulation was significantly reduced after knocking out the CHI3L1 gene [24]. It is also found that CHI3L1 could promote the progression of hepatocellular carcinoma via activating the TGF- β axis, while the number of lung metastases in the mouse model was significantly reduced after inhibiting CHI3L1 [25]. The role and mechanism of CHI3L1 in LF have also been continuously analyzed by more and more scholars. For example, Kang et al. [26] reported that the level of CHI3L1 was significantly positively correlat-

The role of CHI3L1 in chronic hepatitis B liver fibrosis

Table 3. Analysis of risk factors affecting HBeAg-negative CHB liver fibrosis

Factors	β	S.E	Wald	P	OR	95% CI
FIB-4	1.231	0.625	4.361	0.040	3.670	1.087-12.345
GPR	1.563	0.691	5.214	0.022	4.769	1.240-18.376
CHI3L1	2.874	0.767	14.695	<0.001	15.843	4.013-77.674

Note: FIB-4, Fibrosis-4; GPR, gamma-glutamyl transpeptidase to platelet ratio; CHI3L1, Chitinase 3-like 1.

ed with LF deterioration in patients with hepatitis C virus (HCV)-induced chronic hepatitis C, and the decrease of CHI3L1 level could reflect the improvement of LF. Higashiyama et al. [27] confirmed that LF was effectively controlled in mice with defective expression of CHI3L1, and its mechanism was related to the promotion of apoptosis of liver macrophages by CHI3L1 dysregulation.

In our study, HBeAg-negative CHB patients were divided into the non-significant LF group ($F_{0.1}$, $n=38$) and the significant LF group ($F_{2.4}$, $n=40$). Significantly higher serum CHI3L1 expression was determined in the $F_{2.4}$ group compared with that in the $F_{0.1}$ group, suggesting that serum CHI3L1 level may have the potential to diagnose LF in patients with HBeAg-negative CHB. In the research of Li et al. [28], CHI3L1 was significantly overexpressed in patients with HBeAg-positive CHB, which is similar to our research results. Furthermore, LF in patients with HBeAg-negative CHB was found to be closely related to FIB-4, GPR and CHI3L1. We confirmed significant positive correlations of CHI3L1 with FIB-4, GPR and LF staging through correlation analysis, indicating that CHI3L1 mediated the LF process in HBeAg-negative CHB patients and had a significant positive correlation with the severity of LF in such patients. Jiang et al. [11] pointed out that serum CHI3L1 level in CHB patients was positively correlated with FIB-4, which is consistent with our findings. In the report of Schiavon et al. [15], high CHI3L1 and GGT levels and low PLT were significantly associated with HCV fibrosis, while GGT and PLT were used as the denominator and the numerator of GPR, respectively, suggesting that high level of GPR was closely associated with HCV fibrosis and may have synergistic relationship with CHI3L1. Then, through ROC analysis, we found that CHI3L1 had high efficacy in diagnosing LF in HBeAg-negative CHB patients, with the AUC,

optimal cut-off, sensitivity, and specificity of 0.818, 118.2 ng/mL, 80.00%, and 71.05%, respectively. Some studies have shown that the AUC of CHB patients differentiated by CHI3L1 can be as low as 0.73, or as high as 0.97 [11, 13]. We also performed Logistic multifactor regression analysis on the risk factors for LF in HBeAg-negative CHB, and the

data showed that FIB-4, GPR and CHI3L1 were independent risk factors.

This study still has some limitations: (1) The mechanism of action of CHI3L1 has not been investigated, so molecular studies or animal experiments are needed to provide more insight into the molecular mechanism of CHI3L1 against LF. (2) This study did not analyze the diagnostic value of specific fibrosis stages, but only made a preliminary analysis of significant fibrosis and non-significant fibrosis. We will improve the depth of analysis in future research.

All in all, this study proposes for the first time that serum CHI3L1 can be used as a diagnostic marker and risk factor for LF in patients with HBeAg-negative CHB, which provides new insights for the management of this disease.

Acknowledgements

Medical Science and Technology Program of Zhejiang Province, 2019KY764.

Disclosure of conflict of interest

None.

Address correspondence to: Yuecui Li, Department of Infection Diseases, The First People's Hospital of Yongkang, 599 Jinshan West Road, Dongcheng Street, Yongkang 321300, Zhejiang, China. Tel: +86-13819909255; E-mail: yklycwh@126.com

References

- [1] Rao X, Shi HH, Wu ZP, Li XP, Liu XY and Zhang LL. The relationship between serum HBV pgRNA and antigen status in patients with chronic hepatitis B after long-term nucleotide analogues treatment. *Zhonghua Gan Zang Bing Za Zhi* 2021; 29: 766-770.
- [2] Das A, Kamrul-Hasan A, Kabir MR, Das S, Zaki K and Al Mahtab M. Evaluation of Chitinase

The role of CHI3L1 in chronic hepatitis B liver fibrosis

- 3-like 1 (CHI3L1) as a noninvasive biomarker of hepatic fibrosis in patients with hepatitis B virus-related compensated chronic liver disease. *J Family Med Prim Care* 2021; 10: 1694-1698.
- [3] Ahmed FA, Bajaifar MS, Ahmed MA, Alalwan A, Sanai FA, Albeladi K, Aljumah AA and Sanai FM. Quantitative HBsAg levels do not identify hepatic fibrosis in HBeAg-negative chronic hepatitis B patients. *Saudi J Gastroenterol* 2019; 25: 286-292.
- [4] Ouyang Y, Fu XY, Peng SF, Tan DM and Fu L. Plasma miR-146a predicts serological conversion of hepatitis B e-antigen (HBeAg) in chronic hepatitis B patients treated with nucleotide analogs. *Ann Transl Med* 2019; 7: 449.
- [5] Chang XJ, Wang J, Chen Y, Long QH, Song LC, Li Q, Liu HB, Shang QH, Yu ZJ, Jiang L, Xiao GM, Li L, Chen L, Wang XD, Li ZQ, Chen D, Dong Z, An LJ, Tan L, Chen YP and Yang YP. A novel nomogram to predict evident histological liver injury in patients with HBeAg-positive chronic hepatitis B virus infection. *EBioMedicine* 2021; 67: 103389.
- [6] Hu YC, Liu H, Liu XY, Ma LN, Guan YH, Luo X and Ding XC. Value of gamma-glutamyltranspeptidase-to-platelet ratio in diagnosis of hepatic fibrosis in patients with chronic hepatitis B. *World J Gastroenterol* 2017; 23: 7425-7432.
- [7] Xu B, Zhou NM, Cao WT and Li XJ. Evaluation of elastography combined with serological indexes for hepatic fibrosis in patients with chronic hepatitis B. *World J Gastroenterol* 2018; 24: 4272-4280.
- [8] Huang J, Gu ZL, Xu YY, Jiang L, Zhu WG and Wang WW. CHI3L1 (Chitinase 3 Like 1) upregulation is associated with macrophage signatures in esophageal cancer. *Bioengineered* 2021; 12: 7882-7892.
- [9] Zhao T, Su ZP, Li YC, Zhang XR and You Q. Chitinase-3 like-protein-1 function and its role in diseases. *Signal Transduct Target Ther* 2020; 5: 201.
- [10] Yan LL, Deng YQ, Zhou JY, Zhao H and Wang GQ; China HepB-Related Fibrosis Assessment Research Group. Serum YKL-40 as a biomarker for liver fibrosis in chronic hepatitis B patients with normal and mildly elevated ALT. *Infection* 2018; 46: 385-393.
- [11] Jiang ZL, Wang SW, Jin JC, Ying S, Chen ZG, Zhu DD, Xiao BX, Hu YR, Qian YS, Cai T and Fu LY. The clinical significance of serum chitinase 3-like 1 in hepatitis B-related chronic liver diseases. *J Clin Lab Anal* 2020; 34: e23200.
- [12] Huang QY, Wu JH, Huang CS, Wang XL and Xu ZX. A noninvasive diagnostic model for significant liver fibrosis in patients with chronic hepatitis B based on CHI3L1 and routine clinical indicators. *Ann Palliat Med* 2021; 10: 5509-5519.
- [13] Jin X, Fu B, Wu ZJ, Zheng XQ, Hu JH, Jin LF and Tang LL. Serum chitinase-3-like protein 1 is a biomarker of liver fibrosis in patients with chronic hepatitis B in China. *Hepatobiliary Pancreat Dis Int* 2020; 19: 384-389.
- [14] Khare S, Arora A, Sharma P, Dhawan S, Bansal N, Singla V and Kumar A. Performance of non-invasive blood parameters for ruling out significant liver fibrosis in patients with chronic hepatitis B. *J Clin Transl Hepatol* 2020; 8: 143-149.
- [15] Schiavon LL, Narciso-Schiavon JL, Carvalho Filho RJ, Sampaio JP, Medina-Pestana JO, Lanzoni VP, Silva AE and Ferraz ML. Serum levels of YKL-40 and hyaluronic acid as noninvasive markers of liver fibrosis in haemodialysis patients with chronic hepatitis C virus infection. *J Viral Hepat* 2008; 15: 666-674.
- [16] Li Q, Huang CL, Xu W, Hu QK and Chen L. Accuracy of FibroScan in analysis of liver fibrosis in patients with concomitant chronic hepatitis B and nonalcoholic fatty liver disease. *Medicine (Baltimore)* 2020; 99: e20616.
- [17] Ding RR, Zheng JM, Huang D, Wang YB, Li XF, Zhou XL, Yan L, Lu W, Yang ZG and Zhang ZQ. INR-to-platelet ratio (INPR) as a novel noninvasive index for predicting liver fibrosis in chronic hepatitis B. *Int J Med Sci* 2021; 18: 1159-1166.
- [18] Liu JX, Ji YH, Ai H, Ning B, Zhao JZ, Zhang YR and Dun GL. Liver shear-wave velocity and serum fibrosis markers to diagnose hepatic fibrosis in patients with chronic viral hepatitis B. *Korean J Radiol* 2016; 17: 396-404.
- [19] Liu KC, Qin MB, Tao KL, Liang ZH, Cai FQ, Zhao LB, Peng P, Liu SQ, Zou J and Huang JA. Identification and external validation of the optimal FIB-4 and APRI thresholds for ruling in chronic hepatitis B related liver fibrosis in tertiary care settings. *J Clin Lab Anal* 2021; 35: e23640.
- [20] Zhang JL, Du XX, Zhou ZH, Lv FF and Yu YS. Spleen thickness can predict significant liver pathology in patients with chronic hepatitis B with persistently normal alanine aminotransferase or minimally raised alanine aminotransferase: a retrospective study. *J Int Med Res* 2019; 47: 122-132.
- [21] Cao X, Shang QH, Chi XL, Zhang W, Xiao HM, Sun MM, Chen G, An Y, Lv CL, Wang L, Nan YM, Chen CY, Tan ZN, Liu XE and Zhuang H. Serum N-glycan markers for diagnosing liver fibrosis induced by hepatitis B virus. *World J Gastroenterol* 2020; 26: 1067-1079.
- [22] Shan Z, Li LK, Atkins CL, Wang M, Wen YK, Jeong JM, Moreno NF, Feng DC, Gao X, Zhang NY, Lee CG, Elias JA, Lee WM, Gao B, Lam FW, An ZQ and Ju C. Chitinase 3-like-1 contributes to acetaminophen-induced liver injury by promoting hepatic platelet recruitment. *Elife* 2021; 10: e68571.

The role of CHI3L1 in chronic hepatitis B liver fibrosis

- [23] Liu QL, Chen XY, Liu C, Pan JL, Kang XM, Li Y, Du C, Dong S, Xiang AP, Xu Y and Zhang Q. Mesenchymal stem cells alleviate experimental immune-mediated liver injury via chitinase 3-like protein 1-mediated T cell suppression. *Cell Death Dis* 2021; 12: 240.
- [24] Zhang SH, Sousa A, Lin MQ, Iwano A, Jain R, Ma B, Lee CM, Park JW, Kamle S, Carlson R, Lee GG, Elias JA and Wands JR. Role of chitinase 3-like 1 protein in the pathogenesis of hepatic insulin resistance in nonalcoholic fatty liver disease. *Cells* 2021; 10: 201.
- [25] Qiu QC, Wang L, Jin SS, Liu GF, Liu J, Ma L, Mao RF, Ma YY, Zhao N, Chen M and Lin BY. CHI3L1 promotes tumor progression by activating TGF-beta signaling pathway in hepatocellular carcinoma. *Sci Rep* 2018; 8: 15029.
- [26] Kang Q, Chen JH, Luo H, Tan N, Gao H, Zhang XX, Yu M, Liu D, Xi HL, An YY, Han YF, Cheng R and Xu XY. Decrease in chitinase 3-Like protein 1 levels reflects improvement in liver fibrosis after hcv eradication. *Dis Markers* 2020; 2020: 8539804.
- [27] Higashiyama M, Tomita K, Sugihara N, Nakashima H, Furuhashi H, Nishikawa M, Inaba K, Wada A, Horiuchi K, Hanawa Y, Shibuya N, Kurihara C, Okada Y, Nishii S, Mizoguchi A, Hozumi H, Watanabe C, Komoto S, Yamamoto J, Seki S, Miura S and Hokari R. Chitinase 3-like 1 deficiency ameliorates liver fibrosis by promoting hepatic macrophage apoptosis. *Hepatology Res* 2019; 49: 1316-1328.
- [28] Li H, Xu XL, Yi T, Zheng TT and Yan T. Expression of chitinase-3-like protein 1 in different TCM syndromes and its correlation with liver fibrosis. *Ann Palliat Med* 2022; 11: 217-224.