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ORIGINAL ARTICLE

Mutations in basal core promoter is associated with significant fibrosis in both HBeAg positive and negative treatment-naïve chronic hepatitis B

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Summary
Aim: Assessment of liver fibrosis is important for the decision of whether to administrate antiviral treatment in chronic Hepatitis B (CHB) patients. The objective was to investigate the relationship between clinical factors and fibrosis, identify predictors of significant fibrosis in Chinese CHB patients.
Methods: Two hundred and seventy-four treatment-naïve CHB patients (208 HBeAg-positive and 66 HBeAg-negative) who performed transient elastography were consecutively included. We assessed ALT, HBsAg, HBeAg, HBV-DNA, HBV genotype and precore (PC)/basal core promoter (BCP) variants and liver stiffness measurement (LSM) values.
Results: One hundred and nine patients (39.78%) had significant fibrosis ($F \geq 2$, include those with liver cirrhosis). On univariate analysis, significant fibrosis was associated with older age ($P < 0.001$), high ALT levels ($P = 0.003$), lower HBsAg levels ($P < 0.001$), lower HBV DNA levels ($P < 0.001$), HBeAg negative ($P < 0.001$), presence of BCP ($P < 0.001$) and combined BCP/PC mutations ($P = 0.001$). Multivariate logistic regression analysis showed that the strongest

Abbreviations: CHB, chronic hepatitis B; BCP, basal core promoter; PC, precore; LSM, liver stiffness measurement; ALT, alanine aminotransferase; HBsAg, HBV surface antigen.

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independently associated predictors of significant fibrosis ($F \geq 2$) were the presence of HBV BCP mutations ($P < 0.001$) and older age ($P < 0.001$), followed by presence of lower HBsAg ($P < 0.001$), higher ALT levels ($P = 0.006$), PC mutations ($P = 0.011$). The diagnostic accuracy of the combination (age, ALT, HBsAg, BCP/PC variants) model with an area under the receiver-operating characteristic curve of 0.819 (cut-off value was 0.349, $P < 0.001$, 95% CI 0.731—0.914) in predicting significant fibrosis.

Conclusions: We identified four independent risk factors (age, ALT, HBsAg, HBV BCP/PC variants) in predicting significant fibrosis. HBV BCP variants was the strongest predictor of significant fibrosis. The combination of these four variables may facilitate the assessment and management of fibrosis in HBV infected patients.

Introduction

Chronic hepatitis B virus (HBV) infection is a major public health problem. Approximately 350—400 million people worldwide are chronic HBV infection (CHB), and HBV is a leading cause of cirrhosis and associated liver failure, hepatocellular carcinoma (HCC) and death. The clinical course and outcome of CHB was diverse in different individuals. Liver fibrosis is a common complication of CHB leading to the progressive destruction of normal tissue architecture or the replacement of hepatocytic tissue with fibrous tissue. Fibrosis progression is diversified in different individuals and multifactorial because it involves both viral and host factors.

Fibrosis progression in CHB patients was correlated strongly with the level of HBV viral load [1]. CHB patients with high viral load have the highest risk of developing cirrhosis and HCC during long-term follow-up [2], while inactive carriers (viral load < 20,000 IU/mL) have minimal or no liver lesions. Hepatitis B surface antigen (HBsAg) serum level is associated with fibrosis severity in HBeAg-positive patients. HBeAg-positive patients with moderate to severe fibrosis exhibited significantly lower serum HBsAg levels compared with patients with no or mild fibrosis [3]. Both HBV viral load and HBsAg levels are viral factors involved in fibrosis progression. The most common HBV genomic sequence variations include a pre-core stop codon mutation at nucleotide 1896 (G1896A) and double substitution mutations in basal core promoter (BCP) region (A1762T/G1764A), which blocked or reduced HBeAg expression. PC (G1896) and BCP variants (A1762T/G1764A) have been reported to be associated with advanced liver disease and the development of HCC [4]. Furthermore, a recent study performed by Martine Lapalus et al. suggested that PC and BCP variants predict significant fibrosis in CHB patient. However, the ethnicity of this study population was mainly Caucasian and the HBV genotypes were mainly A and D [5]. The influence of HBV genotype on the progression of liver diseases progression has been reported. Studies from Taiwan showed that genotype C was associated with progression to cirrhosis and more frequent occurrence of HCC, while genotype B had a relatively good prognosis. However, whether these HBV variants (G1896A and A1762T/G1764A) with genotype B and C are related to the stage of fibrosis is unknown in Asian.

Assessment of liver fibrosis has become increasingly important in the decision of whether to administrate antiviral treatment in CHB patients. The diagnosis of significant fibrosis ($F \geq 2$) is taken into account for the decision to initiate treatment as by the Chinese Society of Hepatology [6]. Liver biopsy is considered the gold standard for fibrosis progress evaluation. However, the application of liver biopsy is limited due to the features of invasiveness, high cost and potential complications of biopsy procedure. Hence, several noninvasive methods have been developed for diagnosis of liver fibrosis including such as aspartate aminotransferase (AST)-to-platelet ratio index (APRI), transient elastography (FibroScan) and FibroTest [7]. Transient elastography is a rapid, noninvasive, reproducible assessment for detection of liver fibrosis [8]. Liver stiffness measurement (LSM) by FibroScan has been demonstrated to be reliable for detecting advanced liver fibrosis and cirrhosis in CHB [8,9]. FibroScan was recommended for noninvasive assessment of liver fibrosis in CHB by the practice guidelines of APASL [10] and WHO [11]. Therefore, LSM values was used for assessment of liver fibrosis.

The purpose of this study was to evaluate the association between clinical factors and liver fibrosis in treatment-naïve Chinese patients with HBV infection. We aimed to identify independent risk factors for the presence of significant fibrosis ($F \geq 2$) and to develop a CHB specific non-invasive index for predicting significant liver fibrosis ($F \geq 2$), who are suitable candidates for therapy.

Patients and methods

Study design and eligibility patients

A total of 274 treatment-naïve patients with HBV infection in the Center of Infectious Disease of West China Hospital of Sichuan University were consecutively enrolled in this study. Patients were eligible if they had been HBsAg positive for at least six months and never received antiviral therapy within the last 6 months. The exclusion criteria were as follows: