

## Host and Viral Factors Influencing Liver Fibrosis in Chronic HBV Patients with or without Superimposed Steatosis

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### INTRODUCTION

Hepatic fibrosis is the formation of excess fibrous scar connective tissue in liver in a reparative or reactive process. When hepatocytes are injured due to an infection with a virus, heavy alcohol consumption, toxins, nonalcoholic steatohepatitis (NASH) or other factors, the immune system is triggered to repair the damage<sup>[1]</sup>. Hepatic stellate cells (HSCs) are activated in chronic injury by a combination of engulfment of apoptotic bodies and cytokines, leading to hepatic fibrosis with excessive scar tissue building up in the liver<sup>[2]</sup>. Cirrhosis, liver failure, and portal hypertension are well-known complications of advanced hepatic fibrosis<sup>[3]</sup>.

Liver biopsy is considered the gold-standard method for the assessment of liver fibrosis. The degree of fibrosis (stage) usually assess by using scales such as according to the modified histologic activity index (MHAI) of Ishak (stages I-V)<sup>[4,5]</sup> and to the Metavir (stages I-IV) scoring systems<sup>[6-10]</sup>. According to these scales, the degree of fibrosis classifies from 0 to 4 (0: no fibrosis, I: mild; II: moderate; III: severe and IV: cirrhosis).

Fibrosis may co-exist with viral hepatitis B and C. Chronic Hepatitis B virus (CHB) infection is the leading cause of morbidity and mortality, affecting approximately 350 million people worldwide. Globally, 30% of cirrhosis and 53% of primary liver cancer is attributed to HBV infection<sup>[11,12]</sup>. There is increasing data that in patients with chronic hepatitis C (CHC), the presence of fibrosis accompanied by metabolic and viral factors that could increase the severity of fibrosis, and may influence the long-term prognosis of CHC<sup>[7,13-16]</sup>. Unlike to CHC, factors associated with hepatic fibrosis in CHB are not clearly elucidated and there are few studies that include the consecutive groups of patients with chronic viral hepatitis B undergone liver biopsy in order to compare and contrast the factors contributing to hepatic fibrosis.

Hepatic steatosis can influence the progression of chronic liver

### ABSTRACT

In chronic hepatitis B (CHB), the presence of hepatic fibrosis (HF) seems to be associated with known host and viral factors which may influence the long-term prognosis of CHB in the presence or absence of steatosis. We conducted an in-depth review of studies on the host and viral parameters in CHB patients, who acquired biopsy-proven liver fibrosis and we compared and contrasted the factors contributing to HF. In terms of host factors, the presence and stages of fibrosis did not correlate with the levels of FBS, bilirubin, triglyceride, the presence of steatosis, and body mass index. However, older age, prolonged prothrombin time, mild to severe hepatitis activity index (HAI) degree and hepatitis delta co-infection were associated with fibrosis. Other intermediate values for host factors such: as male gender, elevated liver enzyme tests, obesity and heavy alcohol consumption did not meet strong correlation with fibrosis, despite being more common in CHB patients with fibrosis. No significant correlation was found between viral factors (HBV DNA and HBeAg status) and the severity of fibrosis. The severity of fibrosis was not found to be associated with the degree of steatosis of liver in CHB. HF in CHB patients appears to be unrelated to virologic factors. However, fibrosis progression in CHB related to the variable host factors which could be enhanced through these factors in HBV chronic patients.

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diseases to non-alcoholic steatohepatitis (NASH) with development and acceleration of fibrosis. Hepatic steatosis is characterized by the deposition of lipid droplets, mainly triglycerides, in hepatocytes that exceed 5% of the total weight of liver, or excessive fat accumulation in more than 5% of hepatocytes cytoplasm under light microscopic examination<sup>[17,18]</sup>.

Here, we conducted a review study of investigations on patients with CHB, and based on the data collected from patients, we analyzed the host and viral factors that may be associated with the severity of fibrosis in the presence or absence of steatosis.

## METHODOLOGY

In order to clarify the extensive but discrepant data available, we conducted an in-depth review of studies on the prevalence and risk factors for fibrosis in HBV infected patients by search of National Library of Medicines PubMed (NCBI) and Web of Science (ISI) bibliographies of English papers and journals from 2000 to February 2013 on the factors predisposing to fibrosis among chronically HBV-infected patients using the MeSH terms: liver fibrosis and HBV chronic infection along with age, gender, serum biochemistry, BMI, steatosis, alcohol and liver inflammation (specified by HAI index). Hepatic steatosis is one of the investigated variables in the present study. We checked titles and abstracts and eliminated those which were not relevant for the aim of the study or those that did not contain useful information.

We classified the selected papers which contained enough data alphabetically. We included all cross sectional and case-control prospective or retrospective studies. We compared the results of any positive and negative correlation between fibrosis and variables-studied. Then, the impacts of such factors were assessed by the weight of data presented in the literatures.

### Outcomes of Interest and Definitions

The primary outcome was the relationship between fibrosis in CHB patients and host together with viral factors that might be related to the progression of fibrosis. The secondary outcome was the role of steatosis in the severity of fibrosis.

### Inclusion and Exclusion Criteria and Date Extraction

Two reviewers independently screened titles and abstracts for inclusion and exclusion according to the inclusion and the exclusion criteria. The main inclusion criteria were being CHB patients with or without diagnosed steatosis, including common host and viral factors attributed to the fibrosis and those studies that reported risk estimates or provided enough data to allow the estimate calculations. All studies which included HBV/HCV or other viral coinfections along with fibrosis were excluded.

### Statistical Analysis

For calculations, we computed the number of subjects from each study. The qualitative data were evaluated using chi-square test. Continuous variables were expressed as the mean±standard deviation (SD) or median and were compared using independent *t*-test or Mann-Whitney U-test. Results were given in 95% confidence interval and significance was accepted at the *p*<0.05 level.

## RESULTS

### Demographic features and fibrosis

Although older age was independently linked to severe fibrosis in HBV patients in some investigations<sup>[5,14,19,20]</sup>, others did not found strong correlation with the age of patients and the stage of fibrosis<sup>[7,10,21,22]</sup> (Table 1, figure 1). No significant correlation was found between the gender of chronic HBV patients and the severity of fibrosis, despite the number of males was more than females in advanced fibrosis in almost all studies.

### Liver function and fibrosis

Of 9 studies that determined the relationship between the severity of fibrosis and liver enzyme tests (either of ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase), in 3 studies high ALT levels (defined as a value higher than 40 U/L) was independently associated with advanced stages of fibrosis in chronic HBV patients<sup>[10,19,21]</sup>. However, 6 (67%) studies did not find such correlation strongly (Table 1, figure 1). On the other hand, only one out of seven (14%) and one out of three (33%) studies were confirmed the association between high AST and ALP levels and fibrosis in patients-studied, respectively (Table 1, figure 1). Only three available studies did not confirm the association between increased bilirubin and the presence of fibrosis in CHB patients (Table 1, figure 1).

### Serum Fasting Blood Sugar (FBS) and fibrosis

Table 1 and fig 1 show that there was no link to increased fasting blood sugar (FBS) levels and the presence of fibrosis in CHB patients.

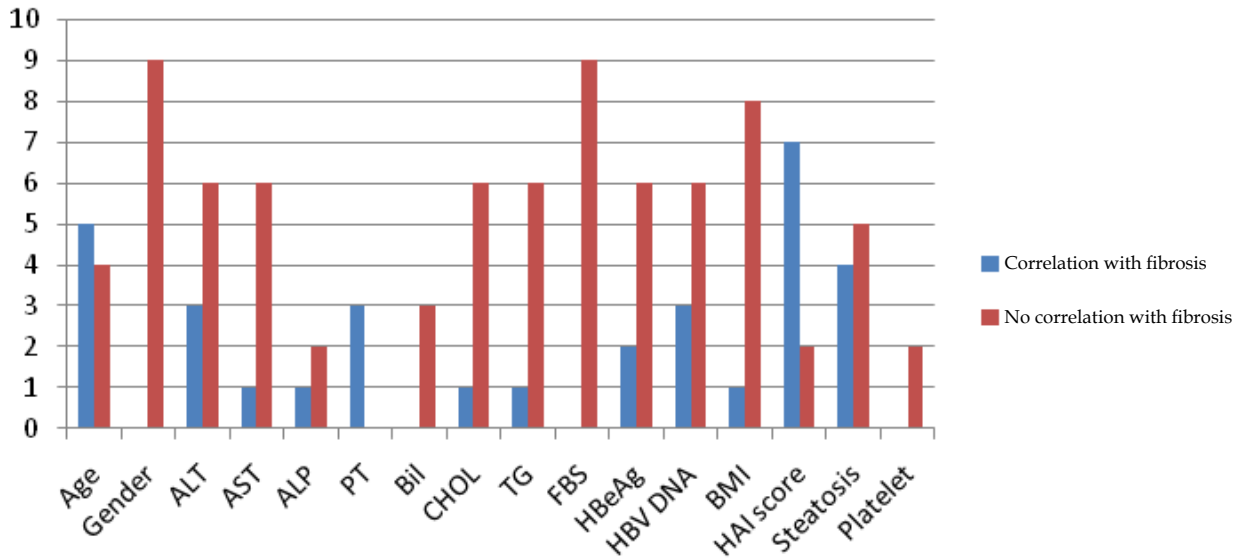
### Serum lipids and fibrosis

Total cholesterol and triglyceride (TG) levels were measured in seven studies (Table 1, figure 1). High levels of cholesterol were not associated with advanced fibrosis in most of included studies in this review (Table 1, figure 1). Considering the levels of TG, our unpublished study (Poortahmasebi *et al*) was the only one that showed its correlation with fibrosis [Odds ratio (OR) 2.005, 95% confidence interval (CI) 1.988-2.022, results not shown].

**Table 1** Host and viral factors associated with hepatic fibrosis in hepatitis B virus (HBV) patients.

Author	Age	Gender	HDV	ALT	AST	ALP	PT	Bil	CHOL	TG	FBS	HBeAg	HBV DNA	BMI	HAI	Steatosis	Obesity(Waist Cir)	Alcohol	Platelet
Peng <sup>[20]</sup>	+	No		No	No	No	+	No	No	No	No	No	+with low DNA	No	+	No	No	No	No
Bondini <sup>[21]</sup>	No	No		+	No						No	No	+with high DNA	No	No	No	+		No
Gordon <sup>[7]</sup>	No	No		No				No	No	No		No	No	No	+	No			+
Petta <sup>[14]</sup>	+	No		No	No			No	No	No	+	No	No	No	+	+			
Thomopoulos <sup>[5]</sup>	+	No		No	No			No	No	No	No	No	No	No	+	No			No
Zheng <sup>[22]</sup>	No	No		No	No			+	No	No	No	No	No	+	No	+			
Yun <sup>[10]</sup>	No	*		+	+	No	+	No	No	No	No	No	No	No	+	+	No	+	No
Shi <sup>[19]</sup>	+	No		+							No	**	+with low DNA	No	****	+			
Poortahmasebi (unpublished)	+	No	+	No	No	+	+	No	No	+	No	No	No	No	+	+			

+: denotes strong association; No: no association; \* Hepatic fibrosis in young men; \*\* Correlation with positive HBeAg; \*\*\* Conversely; fibrosis stage ≥2 were significantly lower in those with steatosis than those without. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; PT: prothrombin time; Bil: bilirubin; CHOL: cholesterol; TG: triglyceride; FBS: fasting blood sugar; HBeAg: hepatitis B e antigen; BMI: body mass index.



**Figure 1** A diagram showing the correlation between the presence and severity of fibrosis with different host and viral factors. The vertical columns indicate the weight of studies presented by the number of investigations. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; PT: prothrombin time; Bil: bilirubin; CHOL: cholesterol; TG: triglyceride; FBS: fasting blood sugar; HBeAg: hepatitis B e antigen; BMI: body mass index.

**Obesity (waist circumference/BMI) and fibrosis**

Body mass index (BMI) usually calculates as the individual's body weight divided by the square of his or her height. According to the new BMI criteria for Asians by the regional office for the western pacific region of WHO (WHO Technical Report Series No. 894, WHO, Geneva, 2000), normal weight, overweight, Obese Class I and Obese Class II were defined by BMI=18.5-22.9 kg/m<sup>2</sup>, 23.0-24.9 kg/m<sup>2</sup>, 25.0-29.9 kg/m<sup>2</sup> and ≥30 kg/m<sup>2</sup>, respectively. Few studies showed the involvement of obesity, either waist circumference<sup>[21]</sup> or BMI<sup>[22]</sup> in the severity of fibrosis. In this regard, the presence of hepatic fibrosis seems not to be associated with the manifestation of abdominal obesity (Table 1, figure 1). However, Thomopoulos *et al.*, assessed the risk factors for steatosis in a study of 233 HBV patients<sup>[5]</sup>. They confirmed that steatosis was independently associated with BMI.

**HBeAg and fibrosis**

A majority of studies showed no correlation between advanced fibrosis and the HBeAg status of the patients (Table 1, figure 1). Only one study undertaken by Shi *et al*<sup>[19]</sup> found that HBeAg positivity was an independent factor linked to the severity of liver fibrosis in HBV chronically infected individuals.

**HBV DNA levels and fibrosis**

The results on the association between the levels of HBV DNA and the severity of liver fibrosis were contradictory (Table 1, figure 1). While most studies did not find such relationship, in two studies, the lower HBV-DNA levels were found to be associated with the severity of fibrosis<sup>[19,20]</sup> (Table 1, figure 1). On the other hand, Bondini *et al* showed that higher HBV-DNA (1.9×10<sup>8</sup> vs. 5×10<sup>6</sup> copies/mL) was associated with the fibrosis in CHB patients<sup>[21]</sup>.

**PT and fibrosis**

The presence of a longer PT seems to be independently linked to more stage of fibrosis, as in all three studies the authors confirmed such involvement (Table 1, figure 1)<sup>[10,20]</sup>.

**Alcohol consumption and fibrosis**

Gordon *et al* showed that alcohol consumption over the preceding 10

years was a significant predictor of hepatic fibrosis (*P*=0.03), while other two studies did not find such association (Table 1, figure 1). Of note that in the latter studies, the heavily alcohol intake CHB patients were excluded from the investigations<sup>[5,20]</sup>.

**Liver necroinflammatory index (HAI) and fibrosis**

Many studies showed that higher stages of fibrosis were associated with moderate to severe necroinflammatory activity (HAI scores), however, others did not found such relationship (Table 1, figure 1).

**Steatosis and fibrosis**

Results for the comparison between steatosis and fibrosis were contradictory and were based on the levels of staging of histopathological findings. By multivariate logistic regression analysis, Petta *et al.* used the cut off of stage >3 (OR 8.187, 95% CI 2.103-31.875)<sup>[14]</sup>. Similarly, however, by univariate analysis we found a significant association (*P*=0.026, Poortahmasebi *et al.*, results not shown). Nonetheless, Zheng *et al* found such strong relationship for only stages 2 (*P*=0.046) and 4 (*P*=0.054)<sup>[22]</sup>. On the other hand, Shi *et al* used ≥2 as a cut off value, and they found that fibrosis were more mild among those with steatosis than those without<sup>[19]</sup>.

**HDV co-infection and fibrosis**

In only one unpublished study by our group, of 160 chronic HBV patients, 10 (6.6%) were positive for hepatitis delta infection. Two of these patients had mild to moderate fibrosis (stage <3). On the other hand, 8 were had severe fibrosis (stage >3). Nonetheless, 17 (10.6%) out of 160 CHB patients had severe fibrosis (stage >3) of whom 8 (47.0%) were positive for HDV. Only 2 (1.4%) out of 143 (89.4%) patients with mild to moderate fibrosis (stage <3) was positive for HDV co-infection (OR 1.892, 95% CI 0.915-2.314 Poortahmasebi *et al.*, unpublished data).

**DISCUSSION**

In the present review, all available data on comparison between either the presence and/or the severity of liver fibrosis from CHB patients and host/viral factors have been collected. In our review we

have determined the effect of hepatic steatosis as one of the effective variables. The presence of hepatic fibrosis seemed not to be associated with HBV factors. On the other hand, host factors such as: older age, prolonged PT and mild to severe HAI degree were associated with fibrosis considering the fact that hepatic fibrosis may be enhanced through these mechanisms in HBV patients. Some host factors like FBS, bilirubin, TG and BMI showed no correlation with advanced fibrosis in CHB patients-studied. We believe that the controversies between medical literatures in this regard, might be related to the selection bias of the patients and the endemicity of HBV in those areas. Other possible reason for such debate could be the influence of HBV genotypes on the outcome of liver disease in different studies, as already described extensively<sup>[23-25]</sup>. There are few data to address this issue. Only two studies compared between A, D (26) and B, C<sup>[27]</sup> genotypes, however, authors did not find any significant correlations between the progression of liver disease and HBV genotypes in CHB plus NASH. On the other hand, this hypothesis has been confirmed strongly by several studies on CHC patients who had concomitant NASH, shown that HCV genotypes correlated with the severity of fibrosis in those patients<sup>[7,28]</sup>.

Contradictory results showed the relationship between fibrosis and other host factors values for this comparison (such as male gender, liver function, obesity and heavy alcohol consumption) in CHB patients. These intermediate host factors did not meet strong correlation with fibrosis; therefore, it might be postulated that CHB might be more vulnerable to the progression of fibrosis in the presence of these intermediate factors. However, the exact mechanisms responsible for the advance liver stage disease in these patients need to be explored.

Regarding the correlation between the fibrosis and steatosis, although there is increasing data shown in patients with CHC, the presence of superimposed non-fatty liver disease (NAFLD), especially concomitant NASH, can be associated with more advanced fibrosis<sup>[21,29]</sup>, many studies have been failed to confirm a consistent link in CHB. Also, it is unclear whether the intracellular distribution of steatosis has a significant effect on and fibrosis in CHB or vice versa. Moreover, fibrosis progression in CHB is variable and related to the extent, severity, duration and frequency of HBV-related hepatic inflammation<sup>[7]</sup> (Table 1). Other possibility might be that steatosis has not been associated with fibrosis stage and that it has been only co-existence disease without negative consequence<sup>[27]</sup>. Besides, elevated ALT and AST levels had no effect on the intensity of fibrosis in these patients. Thus, in contrast to CHC<sup>[5,30]</sup>, the severity of fibrosis was not found to be associated with the degree of steatosis of liver in CHB.

Regarding the data on viral factors (HBeAg and HBV DNA levels), no association was found to relate these factors on the severity of fibrosis in CHB patients. It might be hypothesized that the replication of HBV can decrease when advanced fibrosis is established<sup>[20]</sup>. Another possible explanation for the lack of association could be the fluctuation of HBV replication in HBeAg-negative CHB patients, which means an intermittent progression of necroinflammation and fibrosis<sup>[30,31]</sup>, as many (if not all) the patient-studied were HBeAg negative in studies. However, this hypothesis would need the ability to differentiate active CHB status from nonactive CHB status in longitudinally or perhaps cohort studies to elucidate the relationship between HBV-DNA levels and the severity of fibrosis.

In terms of HDV coinfection, many studies have investigated the impact of HDV on the severity of liver disease in chronic HBV patients and they confirm that HDV accelerates the progression of liver inflammation and fibrosis to cirrhosis and HCC 3-10 times more than HBV mono-infection<sup>[32-34]</sup>. No study compared the impact

of HDV superinfection on the severity of fibrosis in CHB. Our unpublished data showed that the severity (but not the sole presence) of liver fibrosis had a strong correlation with HDV co-infection ( $P < 0.001$ ) (Poortahmasebi, unpublished data). However, due to small size of samples in our study, a definite conclusion needs cohort, longitudinal studies including different groups of CHB patients with mild to severe liver fibrosis with and without HDV co-infection to compare.

In conclusion, the severity of fibrosis was not found to be associated with the degree of steatosis of liver in CHB. A few cross-sectional studies have been carried out so far, thus, longitudinal studies involving serial recording of viral replication status, immune activity, steatosis and progression of hepatic fibrosis is therefore required to more accurately examine the effect of various host and viral factors on fibrosis progression in CHB.

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