

## Role of Liver Biopsy in Patients With Chronic Hepatitis B Who did not Fulfill the Criteria for Immediate Treatment

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**Conflict-of-interest statement:** The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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Received: May 16, 2017

Revised: April 27, 2017

Accepted: April 30, 2017

Published online: August 21, 2017

### ABSTRACT

**AIM:** Lebanon is considered recently as a low endemic country for chronic Hepatitis B. The Aim of our study was to know the METAVIR score in patient with chronic hepatitis B and e negative Ag, who didn't fulfill the local and international treatment criteria, who have HBVDNA > 2000 IU/mL, with normal or slightly elevated ALT level.

**METHODS:** We review all hepatic biopsies done during the last 4 years in patient with chronic Hepatitis B, HBeAg negative, HBV DNA > 2000 IU/ml and ALT within normal range. Collected data were classified and distributed according to METAVIR scoring system for fibrosis and activity, then subdivided according to age, sex and all possible associations between inflammation and fibrosis.

**RESULTS:** A total of 248 liver biopsies were seen during this period,

only 45 biopsies responded to inclusion criteria. The distribution of liver biopsies related to age show that 64% of patients were between 21 and 40 years old, there is a male predominance. The distribution of liver biopsies related to chronic hepatitis B according to the METAVIR score show that 28.86% had advanced fibrosis (stage F2 or more and/or activity A2 or more).

**CONCLUSION:** This study demonstrate the importance of liver biopsy in patients with chronic hepatitis B, HBeAg negative and show that 29% of this group of population need medical treatment for advanced liver disease.

**Key words:** Liver biopsy; ALT; HBeAg negative; Treatment indication

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Rached AA, Saba J, Haykal T, Tabcharani E, Kerbage J, Khairallah S. Role of Liver Biopsy in Patients With Chronic Hepatitis B Who did not Fulfill the Criteria for Immediate Treatment. *Journal of Gastroenterology and Hepatology Research* 2017; **6(4)**: 2400-2404 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/2026>

### INTRODUCTION

Around one third of the world's population has serological evidence of current or past infection with hepatitis B virus (HBV) and 350–400 million people worldwide are chronic carriers of HBV surface antigen. The natural history and the spectrum of diseases of chronic hepatitis B (CHB) infection are variable, ranging from an inactive carrier state to progressive chronic hepatitis B, which may evolve to cirrhosis and hepatocellular carcinoma (HCC)<sup>[1-3]</sup>.

Up to 40% of patients with CHB will develop complications including cirrhosis and/or hepatocellular carcinoma (HCC) during their lifetime<sup>[4]</sup>. While several clinical parameters; including male gender, older age, higher levels of alanine aminotransferase (ALT) and serum HBV DNA level; have been identified as risk factors for severe liver disease<sup>[5-7]</sup>, the gold standard method to assess disease severity remains liver biopsy. Apart from establishing the diagnosis, liver biopsy is often used to assess the severity of the disease in

terms of both stage and grade. Simple histologic staging and grading systems for chronic hepatitis, including the Knodell<sup>[8]</sup>, Ishak<sup>[9]</sup> and METAVIR<sup>[10]</sup> systems, are the most appropriate tools to determine prognosis and to guide clinical management. But the METAVIR score is the most used and accepted globally because it is a simplified system that can be consistently reproducible without significant variation. Worldwide, liver biopsy is recommended for certain CHB patients, especially those with an ALT level of less than 2 times upper limit of normal (ULN)<sup>[11,12]</sup>. In Lebanon, it is indicated in the following groups of patients with CHB: HBeAg positive and HBV DNA fluctuating between 2000 and 20000 IU/mL with ALT>ULN, HBeAg positive and HBV DNA > 20000 IU/mL with ALT 1-2 ULN, HBeAg negative and HBV DNA >2000 IU/mL with ALT 1-2 ULN<sup>[13]</sup>. However, up to 2% of patients develop complications from liver biopsy<sup>[14,15]</sup>.

## PATIENTS AND METHODS

The aim of our study is to determine the percentage of patients with CHB in whom the treatment of hepatitis B is not indicated but they meet the criteria for liver biopsy and subsequently they will be treated when it shows advanced stage of fibrosis or liver activity. Patients are then stratified according to their demographic state (age and sex). All the patients were HBeAg negative which represent more than 90% of chronically infected hepatitis B patients in Lebanon.

All the patients with CHB who underwent liver biopsy at National Institute of Pathology (NIP), for the period extending from January 1, 2010 till December 31, 2014 are included in this study. Collected data were classified and distributed according to METAVIR scoring system for fibrosis (F0, F1, F2, F3, F4) and activity (A0, A1, A2, A3), then subdivided according to age (0-20years, 21-40 years, 41-60 years, > 60 years), sex (female vs. male) and all possible associations between inflammation and fibrosis.

According to results, we calculated the prevalence of each liver stage based on the METAVIR score (fibrosis and inflammation), and the distribution of these stages according to above mentioned criteria.

## RESULTS

Total of 248 liver biopsies related to different hepatic diseases were obtained, 45 biopsies were done for CHB (HBeAg negative). The majority of patients who underwent liver biopsies related to CHB were between 21 and 40 years (64%) with male predominance (64%). The distribution of liver biopsies related to CHB according to the METAVIR score is shown in table 1. The association of different stages of fibrosis and inflammation are shown in the table 2.

In total, 28.86% of patients who underwent liver biopsy are of A2 or more and/or of F2 or more: 24.44% of patient are of A2 or more and 17.76% are of F2 or more. Divided according to sex, we found that 27.6% of males versus 18.75 % of females are of A2 or more; and 17.24% of males versus 18.75% of females are of F2 or more.

## DISCUSSION

In our study, 24.44% and 17.76% had significant inflammation and significant fibrosis respectively. So, 28.86% is a relatively important percentage of CHB patients HBeAg-negative who should be treated after a liver biopsy and/or other non-invasive alternatives to assess liver fibrosis in patients who did not meet the immediate criteria for treatment. This study shows the importance of liver biopsy and/or non-invasive tests for fibrosis assessment for CHB patients, HBeAg-negative who did not fulfill the criteria for immediate treatment.

**Table 1** The distribution of liver biopsies related to CHB according to the METAVIR score.

Inflammation	A0	A1	A2	A3		Total
Number (%)	6(13.33%)	28(62.22%)	4(8.88%)	7(15.55%)		45(100%)
Fibrosis	F0	F1	F2	F3	F4	Total
Number (%)	28(62.22%)	9(20%)	2(4.44%)	1(2.22%)	5(11.11%)	45(100%)

**Table 2** The association of different stages of fibrosis and inflammation.

	Activity			
Fibrosis	A0	A1	A2	A3
F0	5 (11.11%)	19 (42.22%)	3 (6.66%)	1 (2.22%)
F1	0	8 (17.77%)	1 (2.22%)	0
F2	0	0	0	2 (4.44%)
F3	0	0	0	1 (2.22%)
F4	1 (2.22%)	1 (2.22%)	0	3 (6.66%)

For many years, liver biopsy has always been an important tool for the hepatologists for the diagnosis and risk stratification of patients with CHB. Although this procedure carries its risks like bleeding (0.05% to 5.3%) and mortality (0.009% to 0.4%)<sup>[15]</sup>, it is still considered an A1 recommendation and gold standard method for the assessment of liver disease severity according to the most recent EASL guidelines<sup>[16]</sup> and Lebanese guidelines<sup>[13]</sup>. The identification of patients with cirrhosis or advanced fibrosis is of particular importance prior to therapy, as the post treatment prognosis depends on the stage of fibrosis; and the absence of significant fibrosis has important implication for stratification of the disease and the timing of therapy.

The goal of therapy for CHB is to improve quality of life and prolong survival by preventing progression of the disease to cirrhosis, decompensated cirrhosis, end-stage liver disease, HCC and death. This goal is achieved when HBV replication is suppressed in a sustained manner and the subsequent reduction in histological activity of CHB decreases the risk of cirrhosis and HCC, particularly in non-cirrhotic patients<sup>[17]</sup>.

The American Association for the Study of Liver Diseases (AASLD)<sup>[18]</sup>, the European Association for the Study of the Liver (EASL)<sup>[16]</sup> and the Asia-Pacific Association for the Study of the Liver (APASL)<sup>[19]</sup> guidelines determine the patients who should be treated according to specific criteria.

When ALT is less than 2 ULN even with high HBV DNA, liver biopsy is recommended before the initiation of treatment to determine the degree of necroinflammation and fibrosis. In these cases, treatment is indicated if the liver was found in advanced stages of METAVIR fibrosis of F2 or more and activity of A2 or more<sup>[20]</sup>. Available information suggests that patients with persistently normal ALT (PNALT) levels usually have minimal histologic changes and respond poorly, in terms of HBeAg seroconversion, when treated with currently available drugs. Therefore, no drug treatment is recommended for this group of patients unless they have evidence of advanced fibrosis or cirrhosis<sup>[21]</sup>. However, ALT should be followed up every 3 to 6 months<sup>[22]</sup>.

Yuen *et al.* showed that patients with ALT levels of 0.5-1 time ULN and 1-2 times ULN had an increased risk for the development of complications compared with patients with ALT levels less than 0.5ULN ( $p = 0.0001$  for both)<sup>[23]</sup>. A recent Korean long-term follow-up study showed that age and persistent ALT elevation are independent factors for the development of cirrhosis and hepatocellular carcinoma<sup>[24]</sup>. A prospective study conducted in Indonesia over a 3-year period in treatment-naive CHB patients with

ALT  $\leq$  2 ULN. Hepatic histopathology was assessed according to the METAVIR scoring system, significant hepatic inflammation was found in 59.3% of these patients, and significant hepatic fibrosis was found in 62.1%. They concluded that delayed antiviral treatment can be harmful in patients when ALT is less than 2 ULN<sup>[25]</sup>. In China, a retrospective study was done on treatment-naïve CHB patients with persistent normal alanine aminotransferase (PNALT) or elevated ALT with METAVIR scoring system used for histological assessment. In the PNALT group, significant fibrosis was 49.4% and 30.9% in HBeAg - positive and negative patients respectively. Therefore, significant fibrosis is not rare in Chinese CHB patients with PNALT whether regardless of the HBeAg status<sup>[26]</sup>. Another study in central Europe, a total of 253 patients with CHB underwent liver biopsy; they found that patients with CHB and normal transaminases frequently have significant liver fibrosis or cirrhosis (36% and 18 % respectively). Therefore, liver biopsy or liver stiffness measurement (LSM) should be performed in these patients to determine the stage of liver fibrosis<sup>[27]</sup>. Kumar *et al.* showed that a fair proportion of patients with CHB infection with persistent normal ALT have HBV DNA  $\geq$  5 log copies/ml and significant histologic fibrosis<sup>[28]</sup>. A large population study has shown elevated HBV DNA levels in non-cirrhotic HBeAg-negative patients with normal ALT to be associated with an increased risk of HCC<sup>[29]</sup>. In the study of Kim *et al.* showing an increased risk of mortality from liver disease in patients with ALT levels in the upper range of normal, it was suggested that the normal range of serum aminotransferase concentrations should be lowered in populations in which liver disease are common<sup>[30]</sup>. Although patients with persistently elevated ALT levels (70 U/L) may have progression of fibrosis by one stage within 4- 5 years of follow-up<sup>[31]</sup>, others have shown that up to 30% of patients with persistently normal ALT levels may also have significant fibrosis (stage 2-4), can be at increased risk of mortality and may be candidates for therapy<sup>[30,32-36]</sup>. In fact, 37% of patients with persistent normal ALT have significant fibrosis on biopsy<sup>[35]</sup>.

Using such an ALT threshold is open to debate, especially when previous studies had shown CHB patients with a normal ALT at the upper range had an increased risk of long-term cirrhotic complications and HCC<sup>[23,37]</sup>. In patients with only mild elevation of ALT, including those with ALT levels in the upper range of normal, the immune attack on the liver might be more insidious and chronic, leading eventually to more severe and permanent damage<sup>[23]</sup>.

On the other hand, Seto *et al.* demonstrated that there was no significant difference in fibrosis staging among patients with ALT between 1-2 times ULN and ALT more than 2 times ULN regardless of HBeAg status; so, an elevated ALT was not predictive of significant fibrosis<sup>[38]</sup>.

Other studies had demonstrated that there was no good association between ALT levels and fibrosis<sup>[24,39,40]</sup>. Sigal *et al.* also found no correlation of inflammatory activity with clinical, biochemical, or virological parameters<sup>[41]</sup>.

ALT is not a useful marker for the decision of commencing antiviral therapy in CHB because of its poor correlation with significant liver injury in both HBeAg-positive and -negative patients. Patients with ALT levels less than 2 ULN should be considered for possible treatment if histology, or other non-invasive assessment such as transient elastography, shows significant fibrosis. HBeAg-positive CHB with a normal ALT might already have significant histologic abnormalities, which supports the lowering of the current ALT reference ranges. Increased HBV

DNA levels and low platelet count are another factors associated with significant fibrosis in HBeAg-negative disease.

## CONCLUSION

Our study is considered the first to provide prevalence for METAVIR liver fibrosis and activity concerning CHB patients in Lebanon who are in majority HBeAg negative. More than quarter of CHB patients who underwent liver biopsy were found to have advanced stages of METAVIR fibrosis and activity need immediate treatment rather than follow up.

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**Peer reviewer:** Hee Bok Chae