

# Very low probability of significant liver inflammation in chronic hepatitis B patients with low ALT levels in the absence of liver fibrosis

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## Summary

**Background:** Guidelines recommend liver biopsy to rule out significant inflammatory activity in chronic hepatitis B (CHB) patients with elevated hepatitis B virus (HBV) DNA but without other indications for treatment.

**Aim:** To study rates and determinants of clinically significant liver inflammation.

**Methods:** We selected patients with HBV DNA > 2000 IU/mL from the SONIC-B database. The presence of significant inflammation (METAVIR  $\geq$  A2 or HAI  $\geq$  9) was assessed by liver biopsy and correlated with alanine aminotransferase (ALT) levels (according to AASLD upper limits of normal [ULN]) and stratified by the presence of significant liver fibrosis (Ishak  $\geq$  3 or METAVIR  $\geq$  F2).

**Results:** The cohort included 2991 patients; 1672 were HBeAg-positive. ALT was < ULN in 270 (9%), 1-2 times ULN in 852 (29%) and > 2 times ULN in 1869 (63%). Significant fibrosis was found in 1419 (47%) and significant inflammatory activity in 630 (21%). Significant inflammatory activity was found in 34% of patients with liver fibrosis, compared to 9.5% of those without ( $P < 0.001$ ). Among patients without fibrosis, significant inflammatory activity was detected in 3.6% of those with normal ALT, 5.0% of those with ALT 1-2 times ULN and in 13% of those with ALT > 2 times ULN ( $P < 0.001$ ). ALT < 2 times ULN had a negative predictive value of 95% for ruling out significant inflammatory activity among patients without liver fibrosis.

**Conclusions:** Among patients without significant fibrosis, an ALT level < 2 times ULN is associated with < 5% probability of significant inflammatory activity. If fibrosis can be ruled out using non-invasive methods, liver biopsy solely to assess inflammatory activity should be discouraged.

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The authors' complete list of affiliation are present in Appendix 1.

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## 1 | INTRODUCTION

Treatment indications for chronic hepatitis B (CHB) are based on the level of viremia, the severity of liver fibrosis and the severity of liver inflammation.<sup>1,2</sup> Since liver inflammation can only be assessed using liver biopsy, serum ALT levels are widely used for risk stratification. Studies have, however, shown limited correlations between serum ALT levels and histological activity.<sup>3-5</sup> This limitation is of particular relevance for patients with hepatitis B virus (HBV) DNA levels above the treatment threshold (>2000 IU/mL) without signs of significant hepatic fibrosis, since the degree of inflammatory activity would be the primary determinant for commencing anti-viral therapy. Fuelled by various studies suggesting high rates of significant liver inflammation in patients with (near-)normal ALT levels<sup>6,7</sup> as well as persistent rates of clinical events in patients with low ALT,<sup>8</sup> the recent AASLD guidelines suggest to consider liver biopsy to rule out significant inflammatory activity in patients with elevated HBV DNA if there is no treatment indication based on (non-invasively assessed) fibrosis stage.<sup>2</sup> However, the yield of liver biopsy in this context is currently unclear, since previous studies on this topic used lower thresholds to define significant inflammatory activity when compared to current AASLD guidelines, and because older studies also enrolled patients with advanced fibrosis which is currently easily detected by non-invasive methods. The

aim of the current study was therefore to study rates and determinants of clinically significant liver inflammation as defined by AASLD criteria among CHB patients with low levels of ALT, specifically among patients without significant liver fibrosis.

## 2 | PATIENTS AND METHODS

### 2.1 | Patients

The current study used data from the SONIC-B cohort. This cohort includes patients from eight global randomised trials that required baseline liver biopsy and all consecutive CHB patients who underwent liver biopsy in the liver clinics of the Erasmus MC University Hospital in Rotterdam, the Netherlands and the University Health Network, Toronto, Canada. The included trials comprised three studies coordinated by the Foundation for Liver and Gastrointestinal Research from Rotterdam (HBV-9901 study,<sup>9</sup> PARC study,<sup>10</sup> and ARES study<sup>11</sup>), as well as the two phase 3 studies of peginterferon alfa-2a (PEG-IFN) for hepatitis B e antigen (HBeAg)-positive<sup>12</sup> and HBeAg-negative patients,<sup>13</sup> the Neptune study,<sup>14</sup> and the tenofovir disoproxil fumarate (TDF) phase 3 trials.<sup>15</sup> For the current study, we selected patients with (a) HBV DNA levels > 2000 IU/mL and (b) if they had available information on liver inflammatory activity, ALT levels and HBeAg status (Figure 1).

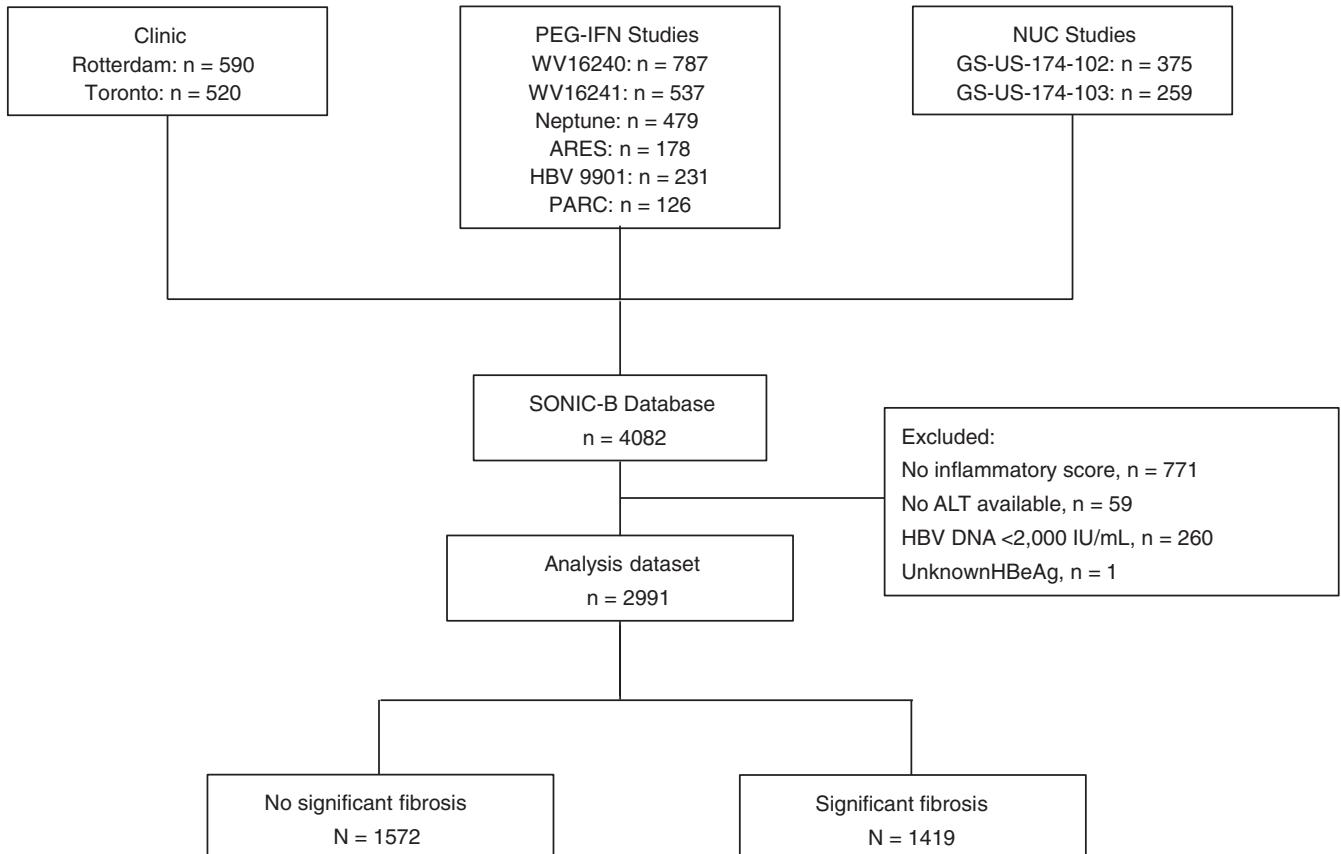


FIGURE 1 Patient disposition

## 2.2 | Laboratory and liver biopsy assessment and definitions

Standard biochemical and virological assessments were performed according to the study and clinical protocols. ALT levels were assessed using local assays, and categorised according to the ULNs as suggested by AASLD (35 U/L for men, 25 U/L for women). Biopsy samples were scored by experienced pathologists. Liver inflammation was scored according to the METAVIR or histologic activity index (HAI) scoring systems. HAI scores were converted to their approximate METAVIR equivalents according to the conversion equation suggested by Rozario et al: HAI scores of 0-3 were considered equivalent to METAVIR A0, HAI scores of 4-8 to METAVIR A1, HAI scores of 9-12 to METAVIR A2 and HAI scores of 13-18 to METAVIR A3.<sup>16</sup> In line with recent AASLD guidelines we defined “moderate liver inflammation” as METAVIR A2 (or HAI 9-12) and severe inflammation as METAVIR A3 (or HAI 13-18).<sup>2,16</sup> Clinically significant inflammatory activity was defined as at least moderate inflammation. Liver fibrosis was defined as no significant fibrosis (Ishak 0-2/METAVIR F0-F1), significant fibrosis (Ishak 3-4/METAVIR F2-F3) or cirrhosis (Ishak 5-6/METAVIR F4).

## 2.3 | Statistical analysis

SPSS version 26 was used for statistical analyses. Data are presented as either mean (SD) or median (interquartile range, IQR) where appropriate. Associations between variables were tested using Student's t-test, Chi-square, Pearson correlation or their non-parametric equivalents when appropriate. Diagnostic performance was assessed with negative predictive values (NPV), sensitivity and specificity and areas under the receiver operator characteristic curve (AUROC). Multivariate analyses were performed using logistic regression.

## 3 | RESULTS

### 3.1 | Patient characteristics

Of the 4082 patients in the SONIC-B cohort, 2991 were eligible for the current analysis (Figure 1). The majority of the patients were of Asian or Caucasian ethnicity. In the overall study population, ALT levels were below the ULN in 270 (9.0%), 1-2 times the ULN in 852 (29%) and > 2 times the ULN in 1869 (63%).

TABLE 1 Patient characteristics

Characteristics	No significant fibrosis (n = 1572)	Significant fibrosis (n = 1419)	P
Demography			
Mean (SD) age, years	34.1 (11.2)	40.4 (12.5)	<0.001
Male	1126 (72%)	1084 (76%)	0.003
Race (n = 2990)			
Caucasian	550 (35%)	598 (42%)	<0.001
Asian	916 (58%)	709 (50%)	
Other	105 (6.7%)	112 (7.9%)	
ALT			
<ULN	168 (11%)	102 (7.2%)	<0.001
1-2 × ULN	505 (32%)	347 (25%)	
>2 × ULN	899 (57%)	970 (68%)	
HBV Genotype (n = 2567)			
A	158 (12%)	196 (17%)	<0.001
B	306 (22%)	154 (13%)	
C	439 (32%)	381 (32%)	
D	427 (31%)	411 (35%)	
Other	49 (3.6%)	46 (3.9%)	
Inflammatory activity			
No inflammation	398 (25%)	87 (6.1%)	<0.001
Mild inflammation	1025 (65%)	851 (60%)	
Moderate inflammation	141 (9.0%)	442 (31%)	
Severe inflammation	8 (0.5%)	39 (2.7%)	

ULN, Upper limit of normal range, defined as 35 for men and 25 for women.

A total of 485 (16%) patients had no inflammation on liver biopsy, 1876 (63%) had mild inflammation, 583 (19%) moderate and only 47 (1.6%) severe inflammation (Table 1 and Table S1). The number of patients with significant (ie at least moderate) inflammation was 9.5% in patients without significant fibrosis, 31% in patients with significant fibrosis and 41% among patients with cirrhosis ( $P < 0.001$ ).

### 3.2 | Relationship between serum ALT levels and liver inflammation

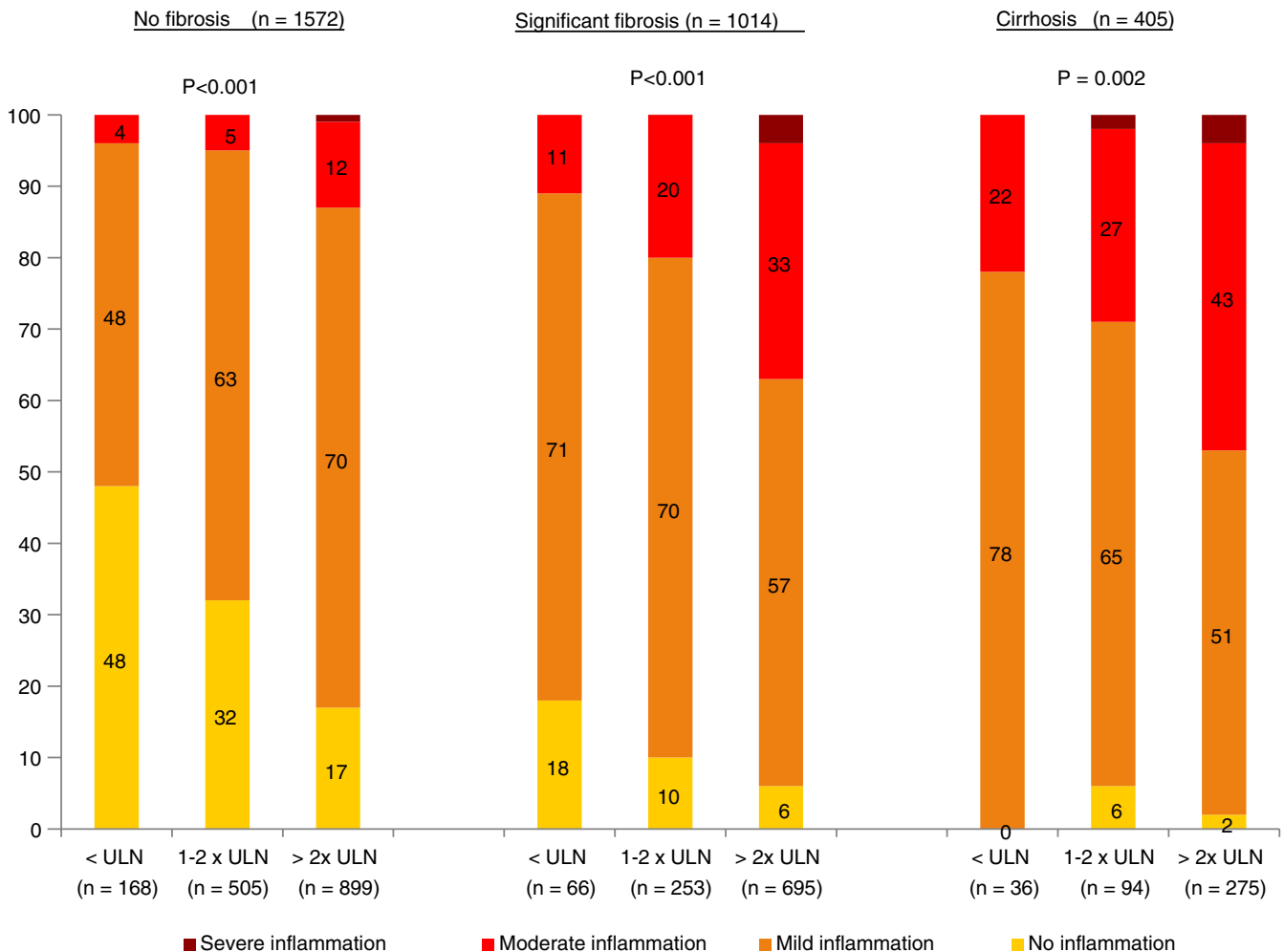
The rates of significant inflammatory activity were higher among patients with ALT levels above two times the ULN, irrespective of fibrosis stage (Figure 2). Among patients with significant fibrosis or cirrhosis, significant inflammatory activity was observed in a substantial proportion of patients with low ALT levels (Figure 2).

Among patients without significant liver fibrosis, none of 168 patients with normal ALT levels and only 1 of 505 (0.2%) of the patients with ALT between 1 and 2 times the ULN had severe

inflammation on liver biopsy. Rates of moderate inflammation were also low among patients with ALT levels below the ULN or between 1 and 2 times the ULN: 3.6 and 4.8%, respectively. An ALT level below two times the ULN therefore had an NPV of 95.4% for ruling out presence of significant inflammatory activity (Figure 2 and 3) among patients without significant liver fibrosis. Findings were consistent in both the trial and clinical cohorts, and across a range of subgroups (Table 2).

### 3.3 | Factors associated with presence of significant (moderate to severe) inflammation

Multivariate analysis confirmed the association between ALT levels and presence of significant liver inflammation with an adjusted odds ratio (aOR) of 3.56 ( $P < 0.001$ ) for ALT levels  $> 2$  times ULN compared to patients with normal ALT levels (Table 3). The presence of liver fibrosis was also independently associated with the presence of significant inflammation (aOR 5.321,  $P < 0.001$ ), as were race, higher



**FIGURE 2** Relationship between ALT levels and inflammatory activity across fibrosis strata. Liver fibrosis was defined as no significant fibrosis (Ishak 0-2/METAVIR F0-F1), significant fibrosis (Ishak 3-4/METAVIR F2-F3) or cirrhosis (Ishak 5-6/METAVIR F4). Liver inflammation was defined as no inflammation (METAVIR A0/HAI 0-3), mild inflammation (METAVIR A1/ HAI 4-8), moderate inflammation (METAVIR A2/ HAI 9-12) or severe inflammation (METAVIR A3/HAI 13-18). HAI: histologic activity index

**TABLE 2** Relationship between ALT levels and significant inflammatory activity in patients without liver fibrosis across subgroups

	No significant inflammation (%)	Significant inflammation (%)	P
<b>Cohort</b>			
Trial cohort (n = 1154)			
ALT < ULN (n = 80)	78 (98)	2 (2.5)	<0.001
ALT 1-2 × ULN (n = 321)	308 (96)	13 (4.0)	
ALT > 2 × ULN (n = 753)	675 (90)	78 (10)	
Clinical cohort (n = 418)			
ALT < ULN (n = 88)	84 (95)	4 (4.5)	<0.001
ALT 1-2 × ULN (n = 184)	172 (93)	12 (6.5)	
ALT > 2 × ULN (n = 146)	106 (73)	40 (27)	
<b>HBeAg status</b>			
HBeAg-positive (n = 920)			
ALT < ULN (n = 76)	74 (97)	2 (2.6)	<0.001
ALT 1-2 × ULN (n = 259)	248 (96)	11 (4.2)	
ALT > 2 × ULN (n = 585)	509 (87)	76 (13)	
HBeAg-negative (n = 652)			
ALT < ULN (n = 92)	88 (96)	4 (4.3)	<0.001
ALT 1-2 × ULN (n = 246)	232 (94)	14 (5.7)	
ALT > 2 × ULN (n = 314)	272 (87)	42 (13)	
<b>Race</b>			
Asian (n = 916)			
ALT < ULN (n = 113)	108 (96)	5 (4.4)	<0.001
ALT 1-2 × ULN (n = 304)	287 (94)	17 (5.6)	
ALT > 2 × ULN (n = 499)	415 (83)	84 (17)	
Caucasian (n = 550)			
ALT < ULN (n = 49)	48 (98)	1 (2.0)	<0.001
ALT 1-2 × ULN (n = 162)	155 (96)	7 (4.3)	
ALT > 2 × ULN (n = 339)	315 (93)	24 (7.1)	
<b>Age</b>			
Age < 30 (n = 696)			
ALT < ULN (n = 64)	63 (98)	1 (1.6)	<0.001
ALT 1-2 × ULN (n = 201)	196 (98)	5 (2.5)	
ALT > 2 × ULN (n = 431)	383 (89)	48 (11)	
Age > 30 (n = 876)			
ALT < ULN (n = 104)	99 (95)	5 (4.8)	<0.001
ALT 1-2 × ULN (n = 304)	284 (93)	20 (6.6)	
ALT > 2 × ULN (n = 468)	398 (85)	70 (15)	

ULN, Upper limit of the normal range, defined as 35 U/L for men and 25 U/L for women.

serum AST levels (in times the local ULN, aOR 1.13,  $P < 0.001$ ) and older age (aOR 1.019,  $P < 0.001$ ).

## 4 | DISCUSSION

Liver biopsy is recommended in CHB management guidelines to rule out significant inflammatory activity in patients with elevated HBV DNA levels (>2000 IU/ml) but without other indications for anti-viral

therapy (ie no signs of hepatic fibrosis and low levels of ALT). In our global multi-ethnic cohort of CHB patients enrolled from two large hepatology clinics and eight global randomised trials, clinically significant (ie moderate to severe) inflammatory activity was detected in < 5% of such patients.

The findings from the current study contradict previous publications which have reported substantial rates of significant liver inflammation even among patients with persistently normal ALT levels.<sup>17-19</sup> These discrepant findings may be explained by the different definitions

of what constitutes “significant” inflammatory activity. Previous studies have used relatively low thresholds to define “significant” inflammatory activity, whereas current AASLD guidelines use a threshold of at least METAVIR A2 (or HAI  $\geq 9$ ). As shown in Figure 2, relatively mild degrees of inflammatory activity may be detected in most patients (in line with previous studies), whereas moderate to severe inflammatory

activity is much less frequently found. Another difference between our cohort and previously published studies is that we were able to stratify by the concomitant presence of liver fibrosis, something that was not possible in smaller studies. In our cohort, the presence of liver fibrosis was associated with the presence of more severe inflammatory activity. This observation is important, since non-invasive tests, such as transient elastography and serum biomarkers, have good diagnostic accuracy for ruling out significant liver fibrosis in HBV infected patients.<sup>20,21</sup> In the current cohort, among 527 patients with FIB-4 < 0.55 (previously shown to rule out advanced fibrosis<sup>21,22</sup>) only 1/72 (1%) patients with normal ALT and only 6/197 (3%) of patients with ALT 1-2  $\times$  ULN had significant inflammation.

**TABLE 3** Factors associated with the presence of significant inflammatory activity on liver biopsy

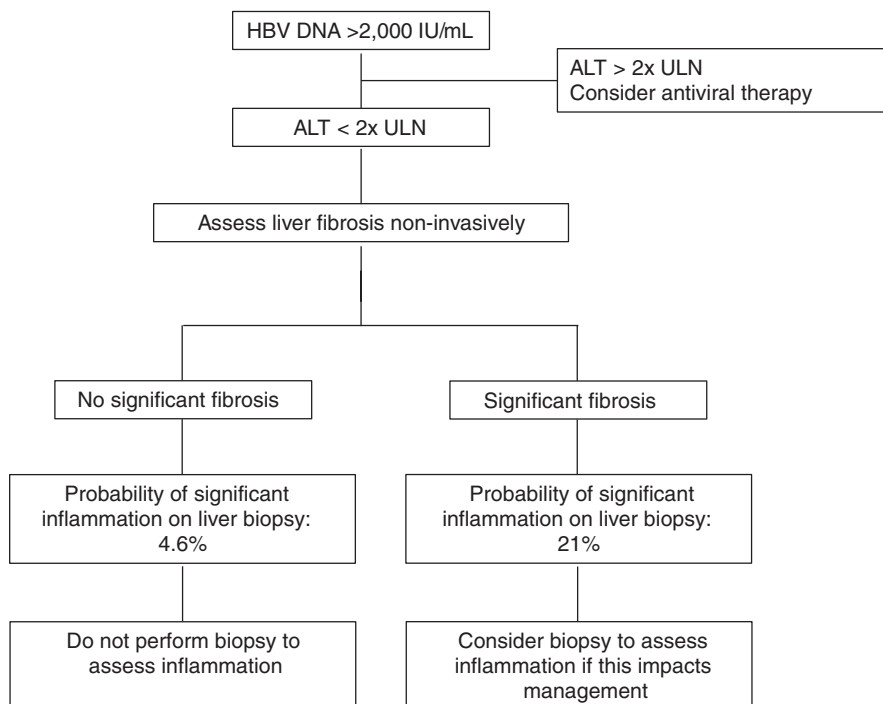
Variable	OR (95% CI)	P
Age	1.019 (1.008-1.029)	<0.001
Sex (male)	1.070 (0.825-1.387)	0.611
HBeAg-positive	0.829 (0.634-1.084)	0.171
Race		
Caucasian	Ref	<0.001
Asian	1.907 (1.489-2.444)	
Other	1.164 (0.740-1.831)	
ALT		
<ULN	Ref	<0.001
1-2 $\times$ ULN	1.560 (0.788-3.088)	
>2 $\times$ ULN	3.555 (1.847-6.841)	
HBV DNA (log c/mL)	1.038 (0.971-1.110)	0.273
AST ( $\times$ ULN)	1.131 (1.073-1.192)	<0.001
Presence of fibrosis <sup>a</sup>	5.321 (4.109-6.892)	<0.001

ULN, times the upper limit of normal. For ALT the ULN is 35 for men and 25 for women.

The local ULN was used for AST.

<sup>a</sup>Ishak  $\geq 3$  or METAVIR  $\geq$  F2.

Once the presence of fibrosis is ruled out, the probability of finding significant inflammatory activity is significantly reduced. In the presence of ALT levels below two times the ULN the risk may be considered extremely low (Figure 3). The yield of liver biopsy in this context therefore appears to be quite limited, and possible benefits are unlikely to outbalance the risks associated with this procedure in most patients. On the other hand, our findings do suggest that liver biopsy could be considered in patients with signs of hepatic fibrosis and low ALT levels (if this would influence the decision to commence anti-viral therapy), since a substantial proportion (>21%) may also have significant inflammatory activity (Figure 3). This is especially important in the light of recent studies that show significant rates of fibrosis progression despite low ALT levels.<sup>23</sup> Furthermore, liver biopsy may be helpful if co-existing liver disease (such as fatty liver disease) is suspected, since the presence of co-existing liver disease, together with other risk factors for adverse outcomes (such as patient age, or a positive family history of cirrhosis or liver cancer) may also impact decision-making concerning the initiation of anti-viral therapy.



**FIGURE 3** Recommendations on performing liver biopsy to assess liver inflammatory activity based on the findings from the current study. ULN, upper limit of normal. Significant fibrosis: Ishak  $\geq 3$  or METAVIR  $\geq$  F2

At this time we have no clear mechanistic explanation as to why the presence of fibrosis impacts the association between ALT levels and liver inflammatory activity, but it is likely there are multiple contributing factors. First, although ALT levels in serum reflect hepatocyte death, there are many types of hepatocyte demise. Different modes of injury and loss may trigger the development of fibrosis through different mechanisms.<sup>24</sup> Differences in the type of hepatocyte injury and loss between patients with and without fibrosis could account for some of the differences observed. Second, current grading systems for liver inflammation are based on histopathological patterns which do not necessarily reflect hepatocyte loss and which therefore correlate rather poorly with ALT levels. Patterns of inflammation might also differ according to the presence or absence of concomitant liver fibrosis, which in turn may result in different histopathological inflammation scores with similar rates of cell death. Unfortunately, this clinical dataset is unable to resolve these issues, and this question requires further investigation.

Strengths of our study include the large international ethnically diverse cohort and therefore the ability to perform stratified analyses. The fact that our observations are consistent among patients enrolled from the clinic as well as in those being screened for treatment trials underscores the robustness, and this is further illustrated by the homogeneity across a range of subgroups. Another potential limitation of the study is the inter-observer variability that has been described with assessment of inflammatory activity. Previous studies have identified the experience of the pathologist as a major determinant of inter-observer agreement.<sup>25</sup> The trials included in this cohort used dedicated pathologists to assess the biopsy slides, as was the case for the two clinical cohorts. Assessment by experienced histopathologists therefore appears to be assured. Also, we defined ALT levels based on a single value. Since we have no longitudinal data we cannot define patients as having "persistently normal" ALT levels. This limitation is unlikely to impact the findings regarding the low risk of significant inflammatory activity in patients without liver fibrosis, since it is probable that rates of significant inflammatory activity are even lower among patients with persistently normal ALT. Further studies in patients with longitudinal follow-up are required to assess histological activity in patients with fluctuating ALT levels. Finally, for the patients being screened for trials some time may have elapsed between liver biopsy and laboratory assessment. We therefore performed sensitivity analyses using only patients with a confirmed biopsy data close to ALT measurement, which were consistent with the findings from the overall study population.

Based on our findings we therefore conclude that among CHB patients without signs of significant fibrosis, the probability of significant inflammatory activity is very low in patients with ALT below two times the ULN. Performing liver biopsy solely for detection of significant inflammatory activity should therefore be discouraged in this group.

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## AUTHORSHIP

*Guarantor of the article:* M.J. Sonneveld.

*Author contributions:* MJS, WPB, BH, RdK, RdM and HLAJ were involved in study design, collection of data, data analysis, writing of the manuscript and approval of final version. HLYC, TP, JDJ, SZ, RC, HC, CW, VP, AG, QX and MB were involved in study design, collection of data, critical review of the manuscript and approval of final version. All authors approve submission of the manuscript.

## DATA AVAILABILITY STATEMENT

Research data are not shared.

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## SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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## APPENDIX 1.

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