Presence of liver fibrosis in chronic hepatitis B patients with varying serum HBV DNA levels

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Author Contributions: Dr. Rui Huang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Supervision: Rui Huang.

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Conflict of Interest
None.
Dear editor,

We read with great interest the article by Kim et al., who investigated the presence of liver fibrosis in chronic hepatitis B (CHB) patients with different hepatitis B virus (HBV) DNA levels. They demonstrated that patients with moderate HBV DNA levels (6–7 log_{10} IU/mL) had the highest aspartate aminotransferase to platelet ratio index (APRI) and fibrosis-4 (FIB-4) scores and an increased risk of hepatocellular carcinoma (HCC) development. These findings suggest that moderate serum HBV DNA level are a significant factor associated with disease progression, providing important insights for the management of patients with CHB. However, the assessment of liver fibrosis was based on noninvasive tests, including APRI and FIB-4, which only have moderate sensitivity and accuracy in identifying hepatitis B-related fibrosis. Currently, liver biopsy remains the gold standard method for assessing liver fibrosis. We analyzed data from a large multicenter cohort of patients with CHB who underwent liver biopsy to assess the presence of liver fibrosis in patients with different serum HBV DNA levels.

A total of 1,058 treatment-naïve patients with CHB who underwent liver biopsy and had alanine aminotransferase (ALT) levels <80 U/L were recruited from four medical institutions (Nanjing Drum Tower Hospital, The Fifth People’s Hospital of Suzhou, The Fifth People’s Hospital of Wuxi, and The Fourth People’s Hospital of Huai’an). The patients were divided into seven groups according to their serum HBV DNA levels. Liver fibrosis was staged using the Scheuer scoring system, with stages (S) ≥2, S ≥3, and S4 defined as significant fibrosis, advanced fibrosis, and cirrhosis, respectively.

The median age of the patients was 40 years and 64.6% were male. The median levels of platelets, ALT, hepatitis B surface antigen (HBsAg), and HBV DNA were 170 × 10^9/L, 33.0 U/L, 3.0 log_{10} IU/mL, and 4.2 log_{10} IU/mL, respectively. Of these, 36.1% were hepatitis B e antigen (HBeAg) negative. A comparison of the clinical features among the patients with different serum HBV DNA levels is shown in Table S1. Overall, patients with HBV DNA levels >7 log_{10} IU/mL were younger, whereas patients in the
HBV DNA 5–6 log_{10} IU/mL and 6–7 log_{10} IU/mL groups had lower platelet counts and higher ALT levels. Most patients with HBV DNA >7 log_{10} IU/mL were HBeAg positive, while all patients with HBV DNA ≤3 log_{10} IU/mL were HBeAg negative. Serum HBsAg levels were positively associated with HBV DNA levels.

In the overall cohort, the proportion of significant fibrosis was highest in patients with HBV DNA 6–7 log_{10} IU/mL (78.7%), followed by patients with HBV DNA 5–6 log_{10} IU/mL (76.4%), ≤3 log_{10} IU/mL (55.7%), 4–5 log_{10} IU/mL (55.6%), 3–4 log_{10} IU/mL (50.7%), 7–8 log_{10} IU/mL group (43.1%), and >8 log_{10} IU/mL (38.2%) (Figure 1A). Patients with moderate HBV DNA levels (6–7 log_{10} IU/mL) also had the highest proportion of advanced fibrosis (51.7%) and cirrhosis (28.1%) (Figure 1B and 1C). We further conducted a subgroup analysis based on HBeAg status. Notably, although 75.4% of patients with HBV DNA 6–7 log_{10} IU/mL had significant fibrosis, the proportion was lower than in patients with HBV DNA 3–4 log_{10} IU/mL (100%) and 5–6 log_{10} IU/mL (81.8%) among HBeAg-positive patients (Figure 1D). Similar results were observed in the proportion of patients with advanced fibrosis and cirrhosis (Figure 1E and 1F). In the HBeAg-negative subgroup, patients with HBV DNA levels of 6–7 log_{10} IU/mL had the highest proportions of significant fibrosis (90.0%), advanced fibrosis (55.0%), and cirrhosis (35.0%) compared to the other groups (P=0.002, P=0.019, and P=0.071, Figure 1G, 1H, and 1I).

Using a large multicenter cohort of patients with CHB, where liver biopsy served as the gold standard method to evaluate liver fibrosis stages, our results suggest that moderate serum HBV DNA levels (6–7 log_{10} IU/mL) are associated with a higher risk of liver fibrosis, particularly in HBeAg-negative patients. These findings are consistent with those of Kim et al. Thus, early initiation of antiviral treatment should be considered for CHB patients with moderate serum HBV DNA levels, even in the absence of liver cirrhosis. However, our study was limited by the lack of adjustment for confounding factors in patients with different HBV DNA levels and included only Chinese patients.
with CHB. Further prospective studies are required to validate these findings.
References


Figure 1. The proportions of significant fibrosis, advanced fibrosis, and cirrhosis in chronic hepatitis B patients with different serum HBV DNA levels.
<table>
<thead>
<tr>
<th>Variables</th>
<th>All patients (n=1,058)</th>
<th>≤3 (n=287)</th>
<th>3-4 (n=211)</th>
<th>4-5 (n=144)</th>
<th>5-6 (n=106)</th>
<th>6-7 (n=89)</th>
<th>7-8 (n=153)</th>
<th>&gt;8 (n=68)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>40.0 (32.0, 48.0)</td>
<td>44.0 (36.0, 51.0)</td>
<td>42.0 (35.0, 49.0)</td>
<td>41.0 (35.0, 48.0)</td>
<td>44.0 (35.8, 50.0)</td>
<td>41.0 (30.0, 47.5)</td>
<td>32.0 (27.0, 38.0)</td>
<td>33.0 (28.0, 37.0)</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Male (%)</td>
<td>683 (64.6)</td>
<td>178 (62.0)</td>
<td>121 (57.3)</td>
<td>104 (72.2)</td>
<td>72 (67.9)</td>
<td>57 (64.0)</td>
<td>100 (65.4)</td>
<td>51 (75.0)</td>
<td>0.041</td>
</tr>
<tr>
<td>PLT (×10⁹/L)</td>
<td>170.0 (132.0, 214.0)</td>
<td>165.0 (130.0, 211.0)</td>
<td>169.0 (131.0, 207.0)</td>
<td>171.0 (135.0, 176.0)</td>
<td>147.0 (110.5, 153.0)</td>
<td>157.0 (103.0, 195.3)</td>
<td>194.0 (155.5, 234.5)</td>
<td>210.0 (182.8, 243.5)</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>33.0 (23.0, 48.0)</td>
<td>25.4 (18.0, 38.0)</td>
<td>25.9 (19.0, 35.1)</td>
<td>37.2 (25.0, 53.0)</td>
<td>42.0 (29.0, 54.3)</td>
<td>44.0 (33.5, 63.5)</td>
<td>41.0 (28.0, 57.3)</td>
<td>40.1 (29.1, 53.7)</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>APRI</td>
<td>0.4 (0.3, 1.0)</td>
<td>0.4 (0.2, 0.5)</td>
<td>0.3 (0.3, 0.5)</td>
<td>0.4 (0.3, 0.6)</td>
<td>0.6 (0.4, 0.8)</td>
<td>0.6 (0.4, 1.1)</td>
<td>0.4 (0.3, 0.6)</td>
<td>0.3 (0.2, 0.4)</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>FIB-4</td>
<td>1.1 (0.7, 1.7)</td>
<td>1.2 (0.8, 1.9)</td>
<td>1.1 (0.8, 1.7)</td>
<td>1.1 (0.8, 1.6)</td>
<td>1.7 (1.1, 2.1)</td>
<td>1.3 (0.8, 2.9)</td>
<td>0.8 (0.6, 1.2)</td>
<td>0.6 (0.5, 0.8)</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>HBeAg positive (%)</td>
<td>382 (36.1)</td>
<td>0</td>
<td>13 (6.2)</td>
<td>29 (20.1)</td>
<td>55 (51.9)</td>
<td>62 (69.7)</td>
<td>149 (97.4)</td>
<td>67 (98.5)</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>HBsAg (log₁₀ IU/ml)</td>
<td>3.0 (2.4, 3.8)</td>
<td>2.6 (2.0, 3.4)</td>
<td>2.9 (2.3, 3.4)</td>
<td>2.9 (2.4, 3.5)</td>
<td>3.1 (2.6, 3.4)</td>
<td>3.0 (2.6, 3.7)</td>
<td>4.4 (3.8, 4.8)</td>
<td>4.4 (4.4, 4.7)</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>HBV DNA (log₁₀ IU/ml)</td>
<td>4.2 (3.0, 6.5)</td>
<td>2.7 (2.3, 2.8)</td>
<td>3.4 (3.2, 3.7)</td>
<td>4.4 (4.2, 4.7)</td>
<td>5.4 (5.2, 5.7)</td>
<td>6.5 (6.2, 6.7)</td>
<td>7.6 (7.3, 7.8)</td>
<td>8.2 (8.1, 8.4)</td>
<td>&lt;0.00</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis-4; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PLT, platelet.