ORIGINAL ARTICLE

Serum hepatitis B surface antigen level might predict cirrhosis and hepatocellular carcinoma in older patients with chronic hepatitis B


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Summary  Background and aim: Distinguishing inactive hepatitis B surface antigen (HBsAg) carriers from hepatitis B e antigen-negative hepatitis remains difficult but is important because patients with active hepatitis may develop severe complications. Long-term follow-up data with stringent criteria are required for the identification of inactive HBsAg carriers. A single serum HBsAg level may be used to solve this difficult diagnostic issue; however, very few studies on its application in older patients have been published. This study was designed to evaluate the clinical significance of a single serum HBsAg level in older patients with chronic hepatitis B (CHB).

Materials and methods: From January 2012 to December 2012, the clinical manifestations of 1749 HBsAg-positive patients were analyzed including 412 patients aged ≥60 years (mean age at enrollment, 68.6 ± 6.9 years; range, 60–90 years; 262 males and 150 females). We investigated the possibility of using a single serum HBsAg level to predict cirrhosis and hepatocellular carcinoma (HCC) in older patients with CHB.

Results: Of the 1749 HBsAg-positive patients, those aged ≥60 years tended to have lower serum HBsAg levels than the younger patients. In fact, all patients aged ≥60 years had a serum * Corresponding author. Division of Gastroenterology and Hepatology, Department of Internal Medicine, Chi-Mei Medical Center, Liouying, Number 201, Taikan, Liouying, Tainan 736, Taiwan.

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HBsAg level \(<10,000\) IU/mL. Of the 412 patients aged \(\geq 60\) years, 122 (29.6%) had cirrhosis and 59 (14.3%) developed HCC. When an HBsAg-titer \(<100\) IU/mL was used to examine severe clinical outcomes (cirrhosis or HCC), the sensitivity, specificity, positive predictive value, and negative predictive value for being free of liver cirrhosis and HCC were 49.3% and 95.2%, 19.7% and 28.8%, 85.6% and 95.2%, and 40.0% and 71.2%, respectively.

**Conclusion:** A single serum HBsAg level \(<100\) IU/mL might predict favorable clinical results in older patients with late-stage CHB virus infection.

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**Introduction**

Chronic hepatitis B (CHB) remains a challenging health problem in Taiwan. More than 3 million people in Taiwan are chronically infected with hepatitis B virus (HBV) and are at high risk of developing hepatic decompensation, cirrhosis, and hepatocellular carcinoma (HCC) [1]. Patients who acquire the infection during the perinatal period or infancy period have three clinical phases, namely, immune tolerant, immune clearance, and inactive residual [2].

However, during the inactive residual phase, CHB reactivation may occur in some patients, which progresses to the fourth reactivation phase (otherwise called the variant phase of immune clearance) [1,3–5]. Patients with reactivation may develop cirrhosis and HCC. Taiwanese studies found a reactivation rate of 2–3% per year and a cumulative rate of 20–25% after 15 years of follow up [4–6].

With stringent criteria including close monitoring of alanine transaminase (ALT) and HBV-DNA levels to avoid misclassification, inactive hepatitis B surface antigen (HBsAg) carrier had excellent outcome [7]. To define a true inactive HBsAg carrier, patients should be followed up regularly for a long period with persistently normal ALT (PNALT) levels and persistently low HBV-DNA levels [8–10].

However, ALT abnormalities may occur due to cofactors (such as alcohol or drugs) rather than HBV reactivation [8,10,11]. The serum HBV-DNA level, which is reflective of HBV replication, is a key factor of disease progression [12]. Stringent monitoring of HBV replication levels in addition to ALT monitoring is more effective in distinguishing between active and inactive HBsAg carriers [7]. However, there are some barriers to monitoring HBV-DNA levels during follow-up evaluations in clinical practice in Taiwan.

The serum HBsAg level has served as a quantitative diagnostic marker for HBV infection and is easy to measure. The relationship between intrahepatic markers of HBV infection (covalently closed circular DNA and integrated HBV DNA) and serum HBsAg levels has been considered a marker of active hepatitis and may predict clinical outcomes [13–17]. Recent studies reported that a single-point evaluation of serum HBV-DNA \(<2000\) IU/mL and HBsAg \(<1000\) IU/mL levels provides complementary information to distinguish between active and inactive HBV genotype D carriers, and the use of a single serum HBsAg level may reflect the clinical stage [18,19].

Older HBsAg-positive patients who acquired HBV infection during the perinatal or childhood period represented either late-stage inactive HBsAg carriers or those with CHB reactivation. Patients with low-serum HBsAg levels in the later stage of CHB infection may be long-term inactive HBsAg carriers and have a favorable outcome. We conducted this study to evaluate the clinical significance of a single serum HBsAg level in predicting favorable clinical outcomes in older patients who live in areas highly endemic for CHB.

**Materials and methods**

**Study populations**

Liouying is located in the northern part of Tainan County, which is an area in southern Taiwan with hyperendemic HBV infection [20]. The Chi-Mei Medical Center in Liouying is a tertiary hospital that receives patient referrals for antiviral therapy for CHB. The majority of its patients live in the northern part of Tainan County.

This study was approved by the Ethics Committee of Chi-Mei Medical Center. Between January 2012 and December 2012, 1749 HBsAg-positive patients (serum HBsAg level \(\geq 0.05\) IU/mL) were followed up at our hospital. The serum HBsAg levels of the patients with a history of hepatitis B confirmed by a qualitative test for HBsAg positivity before January 1, 2012, were measured during the study period. In addition, patients who were suspected to have hepatitis or underwent hepatitis B screening for any reason during the study period underwent evaluation of serum HBsAg levels.

**Table 1** presents the serum HBsAg levels of patients in different age groups. Patients without available anti-hepatitis C virus (anti-HCV) data, those aged \(\leq 60\) years, or those with both hepatitis B and C virus infections were excluded. Finally, a total of 412 patients were enrolled and their clinical manifestations were analyzed. Patients’ ages and their clinical manifestations were retrieved from medical records for analysis. Because acute hepatitis B is rare in older individuals in this highly endemic area, CHB was diagnosed if a single serum HBsAg test result was positive. Serum HBsAg levels were tested for abnormal ALT level or hepatitis history in 318 patients, before chemotherapy in 74 patients, and for routine admission in 20 patients. None of the patients received antiviral therapy before their serum HBsAg levels were tested.

The definition of PNALT was that all ALT data that had been checked in our hospital were within normal limits because the examination intervals differed among inactive
carriers, patients with active hepatitis, and patients with cirrhosis. We grouped patients into cirrhotic and non-cirrhotic groups, which included inactive carriers and patients with active hepatitis because it was difficult to identify inactive carriers in this cross-sectional study. The severe clinical outcomes included patients who had HCC and/or cirrhosis. Cirrhosis was diagnosed using ultrasonographic features and procedures based on the criteria reported by Lin et al [21]. HCC was diagnosed by two of the three following imaging methods: ultrasonography, computed tomography, and magnetic resonance imaging with typical HCC imaging.

Laboratory tests

Serological and biochemical examinations

The level of alanine aminotransferase (normal upper limit, 50 IU/L) was measured on a multichannel autoanalyzer (Hitachi-7600; Tokyo, Japan). HBsAg and second-generation HCV antibody were detected using commercially available enzyme-linked immunosorbent assay kits (Abbott, North Chicago, IL, USA). HBsAg was monitored using chemiluminescent microparticle immunoassay (ARCHITECT HBsAg, Abbott Laboratories, Barceloneta, Puerto Rico; quantitative limit between 0.05 and 250 IU/mL). The samples were diluted to maintain titer > 250 IU/mL when necessary. The HBV-DNA levels were investigated in the serum samples using the real-time polymerase chain reaction technique (COBAS AmpliPrep and TaqMan HBV Test; Roche, Mannheim, Germany; quantitative limit between 12 and 110,000,000 IU/mL).

Statistical analyses

Discrete variables were expressed as numbers (n) and frequency (%), and statistically tested using the Chi-square test or Fisher exact test. Continuous variables were expressed as mean ± standard deviation and were statistically tested by the two-tailed Student t test. All p values < 0.05 were considered statistically significant.

Results

A total of 412 patients (mean age at enrollment, 68.6 ± 6.9 years; range, 60–90 years; 262 males and 150 females) were enrolled in this study. Patients aged ≥ 60 years tended to have lower serum HBsAg levels (Table 1), and none had a serum HBsAg > 10,000 IU/mL.

Among the patients participating in our study, 322 (78.2%) patients were screened for hepatitis B e antigen (HBeAg) and 307 (95.0%) were HBeAg negative. Of the HBeAg-positive patients, 12 of 15 (80%) patients were aged 60–69 years (Table 2).

A total of 245 (59.5%) patients had a serum HBsAg level > 100 IU/mL, including a subgroup of 113 (27.4%) patients whose HBsAg levels were > 1000 IU/mL. The proportions of patients with the HBsAg level > 100 IU/mL were evenly distributed among the age groups of 60 years, 70 years, and 80 years (Table 2). A total of 143 (34.7%) patients had elevated ALT and there were no significant differences among patients in the different age groups (Table 2).

Severe clinical outcomes were found in 122 (29.6%) patients with cirrhosis and in 59 (14.3%) patients who developed HCC. Severe clinical outcomes were evenly distributed between patients in the different age groups. However, the proportion of patients with cirrhosis increased from 26.8% in the 7th decade to 36.1% in the 9th decade of life (p < 0.05; Table 2). Twenty-three percent (98/412) of patients had cirrhosis and an HBsAg level > 100 IU/mL, whereas 5.8% (24/412) had cirrhosis and an HBsAg level < 100 IU/mL (p < 0.0001). When a serum HBsAg level < 100 IU/mL was used to predict whether patients were free of liver cirrhosis, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 49.3%, 19.7%, 85.6%, and 40.0%, respectively. When this criterion was used to predict whether patients were free from HCC, the sensitivity, specificity, PPV, and NPV were 95.2%, 28.8%, 95.2%, and 71.2%, respectively (Table 3).

When a serum HBsAg level > 100 IU/mL was used to predict liver cirrhosis, the sensitivity and NPV were 80.3% and 85.6%, respectively. When this criterion was used to predict HCC, the sensitivity, specificity, PPV, and NPV were 71.2%, 4.8%, 71.2%, and 95.2%, respectively (Table 3).

A total of 216 (52.4%) patients underwent HBV-DNA level examination within 1 month of the HBsAg level assessment. Of these patients, 66.7% had an HBV-DNA level > 2000 IU/mL (Table 2). We did not analyze the predictive value of the serum HBsAg level combined with the HBV-DNA level, because the latter was not available for half of the enrolled patients.

Table 1  Proportion of the serum HBsAg level in patients with chronic hepatitis B by different age subgroups.

<table>
<thead>
<tr>
<th>Age</th>
<th>&lt;20 y</th>
<th>20–29 y</th>
<th>30–39 y</th>
<th>40–49 y</th>
<th>50–59 y</th>
<th>60–69 y</th>
<th>70–79 y</th>
<th>&gt;80 y</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>M:F</td>
<td>0.67</td>
<td>0.86</td>
<td>1.42</td>
<td>1.73</td>
<td>1.67</td>
<td>1.71</td>
<td>1.46</td>
<td>1.63</td>
<td></td>
</tr>
<tr>
<td>&lt;1 L</td>
<td>1</td>
<td>(20)</td>
<td>6</td>
<td>(9)</td>
<td>42</td>
<td>(12)</td>
<td>54</td>
<td>(14)</td>
<td>85</td>
</tr>
<tr>
<td>1–2 L</td>
<td>0</td>
<td>(10)</td>
<td>15</td>
<td>(30)</td>
<td>64</td>
<td>(17)</td>
<td>78</td>
<td>(17)</td>
<td>171</td>
</tr>
<tr>
<td>2–3 L</td>
<td>1</td>
<td>(20)</td>
<td>6</td>
<td>(9)</td>
<td>72</td>
<td>(21)</td>
<td>84</td>
<td>(22)</td>
<td>137</td>
</tr>
<tr>
<td>3–4 L</td>
<td>1</td>
<td>(20)</td>
<td>25</td>
<td>(38)</td>
<td>144</td>
<td>(42)</td>
<td>143</td>
<td>(38)</td>
<td>140</td>
</tr>
<tr>
<td>4–5 L</td>
<td>2</td>
<td>(40)</td>
<td>15</td>
<td>(23)</td>
<td>48</td>
<td>(14)</td>
<td>27</td>
<td>(7)</td>
<td>10</td>
</tr>
<tr>
<td>5–6 L</td>
<td>0</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>451</td>
</tr>
</tbody>
</table>

HBsAg = hepatitis B surface antigen.
Serum HBsAg level might predict cirrhosis and HCC

Table 2  Clinical manifestations in patients with chronic hepatitis B by different age subgroups.

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>&gt;60 y</th>
<th>60–69 y</th>
<th>70–79 y</th>
<th>&gt;80 y</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>412</td>
<td>250</td>
<td>126</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Follow up (mo)</td>
<td>82.71 ± 75.43</td>
<td>82.41 ± 55.74</td>
<td>83.45 ± 109.63</td>
<td>82.14 ± 42.13</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>M:F</td>
<td>1.7</td>
<td>1.7</td>
<td>1.8</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>68.6 ± 6.9</td>
<td>64.0 ± 2.8</td>
<td>73.5 ± 2.6</td>
<td>83.8 ± 2.9</td>
<td></td>
</tr>
<tr>
<td>HBsAg (IU/mL)</td>
<td>1153.2 ± 4256.9</td>
<td>1435.3 ± 5340.1</td>
<td>752.8 ± 1476.4</td>
<td>595.1 ± 814.1</td>
<td>0.05</td>
</tr>
<tr>
<td>HBsAg &gt; 100 IU/mL</td>
<td>245 (59.5)</td>
<td>156 (62.4)</td>
<td>66 (52.4)</td>
<td>23 (63.9)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>HBsAg &gt; 1000 IU/mL</td>
<td>113 (27.4)</td>
<td>74 (29.6)</td>
<td>30 (23.8)</td>
<td>9 (25.0)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>HBeAg (n)</td>
<td>322 (78.2)</td>
<td>206 (82.4)</td>
<td>93 (73.8)</td>
<td>23 (63.9)</td>
<td></td>
</tr>
<tr>
<td>HBeAg (−)</td>
<td>307 (95.3)</td>
<td>194 (90.7)</td>
<td>91 (97.8)</td>
<td>22 (95.7)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>HBV DNA (log)</td>
<td>7.25 ± 8.26</td>
<td>6.81 ± 7.45</td>
<td>6.65 ± 7.39</td>
<td>8.21 ± 8.81</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>&gt;2000 IU/mL</td>
<td>144/216 (66.7)</td>
<td>104/147 (70.7)</td>
<td>27/53 (50.9)</td>
<td>13/16 (81.3)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>ALT (IU/mL)</td>
<td>105.4 ± 252.7</td>
<td>117.6 ± 287.5</td>
<td>64.5 ± 119.0</td>
<td>163.7 ± 317.6</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>ALT &gt; 50</td>
<td>154 (37.4)</td>
<td>97 (38.8)</td>
<td>40 (31.7)</td>
<td>17 (47.2)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>PNALT</td>
<td>143 (34.7)</td>
<td>80 (32.0)</td>
<td>50 (39.7)</td>
<td>13 (36.1)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>LC and HBsAg &gt; 100 IU/mL</td>
<td>122 (29.6)</td>
<td>67 (26.8)</td>
<td>42 (33.3)</td>
<td>13 (36.1)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>LC and HBsAg &lt; 100 IU/mL</td>
<td>98 (23.8)</td>
<td>48 (20.9)</td>
<td>24 (19.0)</td>
<td>5 (13.9)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>HCC</td>
<td>42 (10.2)</td>
<td>17 (4.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC and HBsAg &gt; 100 IU/mL</td>
<td>59 (14.3)</td>
<td>30 (12.0)</td>
<td>24 (19.0)</td>
<td>5 (13.9)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>HCC and HBsAg &lt; 100 IU/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALT = alanine transaminase; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; LC = liver cirrhosis; PNALT = persistently normal alanine transaminase level.

Discussion

In Asia, HBeAg seroconversion tends to occur in patients aged 30–35 years, and most patients (90%) develop it before the age of 40 years [22–25]. In our study, patients enrolled were all aged ≥ 60 years and 90% of them were HBeAg negative, which supported this observation. Among patients developing HBeAg seroconversion before the age of 30 years, only a very low portion will experience relapse. However, a higher proportion of patients who experience HBeAg seroconversion after the age of 40 years will experience relapse [26,27]. A Taiwanese study reported that 20–25% of patients developed recurrent active hepatitis during a 15-year follow-up period and these patients tended to develop cirrhosis or HCC [4,28–32]. Our study, which included patients in the later stage of CHB, found that 29.6% of patients had cirrhosis, which supported previous results.

One stringent criterion used to identify patients who are inactive HBsAg carriers resulted in the identification of only a limited number of patients in longitudinal cohort studies [7]. In our study, 30–40% of the patients had PNALT, and ALT level fluctuation may be caused by cofactors and do not necessarily indicate CHB severity.

HBV replication that is reflected by the serum HBV-DNA level is the key factor of disease progression [12]. According to the National Institutes of Health and the European Association for the Study of the Liver guidelines, the differentiation between inactive and active phases of HBeAg-negative CHB is based on an HBV-DNA cutoff level of 2000 IU/mL. These criteria, however, led to some controversial results [14,33,34]. Thus, stringent monitoring of HBV replication levels in addition to ALT levels to avoid misclassification of the HBV infection profile caused by HBV-DNA level fluctuations during cross-sectional evaluation was recommended [7,31]. Patients with an HBV DNA >

Table 3  Cutoff values for predicting freedom from liver cirrhosis or hepatocellular carcinoma.

<table>
<thead>
<tr>
<th></th>
<th>HBsAg &lt; 100 IU/mL (%)</th>
<th>HBsAg &gt; 100 IU/mL (%)</th>
<th>HBsAg &gt; 1000 IU/mL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver cirrhosis</td>
<td>Sensitivity: 49.3</td>
<td>Specificity: 19.7</td>
<td>PPV: 85.6</td>
</tr>
</tbody>
</table>
| HCC | Sensitivity: 5340.1 | Specificity: 752.8 | PPV: 27.4 | NPV: 156.7 | Sensitivity: 1476.4 | Specificity: 595.1 | PPV: 1000 IU/mL versus LC and HBsAg > 100 IU/mL; p < 0.001; HCC and HBsAg > 100 IU/mL versus HCC and HBsAg < 100 IU/mL: p < 0.05.

HBsAg = hepatitis B surface antigen; HCC = hepatocellular carcinoma; PPV = positive predictive value; NPV = negative predictive value.
2000 IU/mL had a predisposition for hepatic flares [31,32]. However, patients with PNALT may have HBV-DNA levels > 20,000 IU/mL, and this finding supports the recommendation of monitoring the HBV-DNA level in addition to the ALT levels to define the inactive HBsAg carrier state [4,5,32]. All of these studies demonstrated the limitation of using a single serum HBV-DNA level or ALT monitoring to predict inactive carrier status.

Studies have shown that serum HBsAg levels are higher in patients with active HBeAg-negative chronic hepatitis than in inactive carriers, and that a single serum HBsAg level may predict the clinical status of HBV infection [19,34–37]. These studies also revealed the association between HBsAg levels and liver inflammation and fibrosis [19,37]. An Italian study of HBeAg-negative carriers found that an HBsAg level < 1000 IU/mL was strongly associated with the inactive HBsAg carrier state [34]. Another Taiwanese study indicated that measuring HBsAg levels may improve the identification rate of patients who are at increased risk of developing CHB-related complications [36]. The combined use of HBV-DNA and serum HBsAg levels monitoring may improve prediction of clinical stages and complications in cross-sectional studies [35–37].

In our study, the serum HBsAg levels tested before the patients received antiviral therapy were all <10,000 IU/mL and lower levels were found with increasing age. The proportion of liver cirrhosis and HCC is lower in patients with an HBsAg level < 100 IU/mL (p < 0.001 and p < 0.05, respectively). The criterion that an HBsAg level < 100 IU/mL, but not < 1000 IU/mL, had a high predictive value for predicting freedom from cirrhosis and HCC at the time the HBsAg level was examined. Using serum HBsAg levels to predict CHB severity revealed a discrepancy between our study results and those of European studies. This discrepancy may be due to differences in age or genotype. Most longitudinal studies of inactive HBsAg carriers enrolled patients in their 30s or 40s and followed them for 3–20 years [7]. These studies recruited fewer older patients in the late stage of CHB infection. The serum HBsAg level can be considered a surrogate marker for the number of infected cells. As time progresses, a lower serum HBsAg level may indicate less HBV replication or fewer infected hepatocytes in patients with better prognosis. Lower serum HBsAg levels in old age may occur in patients who were active carriers in the early part of their life. However, the long-term effect of HBV-DNA concentration fluctuation and the correlation between HBV-DNA and serum HBsAg levels in older patients require further study.

A genotype that might have an impact on HBsAg production is another factor that may affect the prediction of clinical results using the serum HBsAg level. In fact, lower HBsAg levels have been observed in East Asian patients carrying HBV genotypes B and C [19]. In Taiwan, the major genotypes of HBV are B and C, and the serum HBsAg levels would be lower than those observed in European patients.

In a Taiwanese study, 23% of patients with HBeAg-negative and HBV-DNA-positive reactive hepatitis developed cirrhosis during the 9-year follow-up period [4]. In our study, 30% of patients developed cirrhosis prior to enrollment. Fourteen percent (24/167) of patients with an HBsAg < 100 IU/mL had cirrhosis; these patients may have severe liver inflammation during the immune clearance stage. Only 34.7% of patients had PNALT. However, the limitation related to ALT in this study involves different frequencies of ALT examination due to varying clinical severities. In daily practice in Taiwan, the follow-up duration differs among patients with and without cirrhosis. More than 60% of patients who underwent the HBV-DNA test had a serum level > 2,000 IU/mL. Older patients in our study tended to develop cirrhosis, and these results indicated that older patients with active HBeAg-negative hepatitis would have a lower chance of remission and need aggressive treatment.

The combined use of HBV-DNA and serum HBsAg levels may improve the prediction in cross-sectional studies. However, these results did not improve when we analyzed the value of combined HBV-DNA and serum HBsAg levels in the subgroup of patients who underwent HBV-DNA testing (data not shown). Because HBsAg-positive patients in Taiwan are not routinely screened for HBV-DNA levels, we did not have these data available for all patients, which is a study limitation. The other limitation of this study was that data on other factors that may contribute to the development of cirrhosis (e.g., diabetes mellitus or autoimmune hepatitis) were not available. Results from our study showed that a single HBsAg serum level < 100 IU/mL may predict favorable clinical results in older patients in the late stage of CHB virus infection. Antiviral therapy may affect the serum HBsAg level, and the effectiveness of clinical outcome prediction using the serum HBsAg level needs further study.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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