What have we learned from HBV clinical cohorts?

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Clinical outcomes of Asian HBV carriers

Adverse outcome

Asian HBV carrier

Favorable outcome

What are factors affecting long-term outcomes?

### Factors associated with disease progression in Asian HBV carriers

<table>
<thead>
<tr>
<th>Viral</th>
<th>Host</th>
<th>Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent presence of HBeAg</td>
<td>Male gender</td>
<td>Heavy drinking</td>
</tr>
<tr>
<td>Persistently high HBV-DNA level</td>
<td>Increasing age</td>
<td>Cigarette smoking*</td>
</tr>
<tr>
<td>HBV genotype C &gt; genotype B</td>
<td>Recurrent ALT flare</td>
<td>Aflatoxin*</td>
</tr>
<tr>
<td>Core promoter mutations*</td>
<td>Persistently increased ALT levels</td>
<td>HCV, HDV, or HIV co-infection</td>
</tr>
<tr>
<td>High HBsAg level**</td>
<td>Cirrhosis*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes*</td>
<td></td>
</tr>
</tbody>
</table>

*Factors shown to be associated with an increases risk of HCC only. Abbreviations: ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HCC, hepatocellular carcinoma.

** In HBV carriers with HBV DNA < 2000 IU/mL

Outline

- HBV natural history cohorts
  - REVEAL-HBV
  - SEARCH-B
  - ERADICATE-B
- Risk calculator update
- Conclusions
### Summary of three HBV cohorts

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Study design</th>
<th>Disease stage</th>
<th>Number of participants</th>
<th>Follow-up (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>REVEAL-HBV</td>
<td>Community-based cohort</td>
<td>Including HBeAg-positive and -negative phases</td>
<td>3653</td>
<td>11.4</td>
</tr>
<tr>
<td>SEARCH-B</td>
<td>Hospital-based cohort</td>
<td>Early HBeAg negative phase</td>
<td>390</td>
<td>7.4</td>
</tr>
<tr>
<td>ERADICATE-B</td>
<td>Hospital-based cohort</td>
<td>Including HBeAg-positive and -negative phases</td>
<td>2688</td>
<td>14.7</td>
</tr>
</tbody>
</table>

**REVEAL-HBV** = Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus  
**SEARCH-B** = Study of E Antigen seRoClearance of Hepatitis B  
**ERADICATE-B** = Elucidation of Risk Factors for Disease Control or Advancement in Taiwanese Hepatitis B Carriers

Flow of REVEAL-HBV cohort

1. 89,293 individual from 7 townships invited to participate in 1991-1992
2. 23,820 enrolled in study
3. 4,155 HBsAg seropositive
4. 3,851 adequate blood sample for HBV viral load and genotype
5. 3,653 for REVEAL-HBV study
6. 65473 decided not to participate
7. 19665 excluded due to HBsAg seronegative
8. 304 excluded due to inadequate blood sample for tests of HBV viral load
9. 198 excluded (195 anti-HCV seropositive; 3 lacked adequate sample for anti-HCV test)

References:
2. Yang HI et al. JCO 2010;28:2437-2444

Kao 2015
High baseline HBV DNA associated With increased risk of HCC and cirrhosis

REVEAL: Long-term follow-up of untreated community-based HBsAg+ve individuals in Taiwan

Cumulative Incidence of HCC at Year 13 Follow-up\(^1\) (N = 3653)

- < 300: 1.3%
- 300-9999: 1.4%
- 10,000-99,999: 3.6%
- 100,000-1 million: 12.2%
- ≥ 1 million: 14.9%

Cumulative Incidence of Cirrhosis at Year 13 Follow-up\(^2\) (N = 3582)

- < 300: 4.5%
- 300-9999: 5.9%
- 10,000-99,999: 9.8%
- 100,000-1 million: 23.5%
- ≥ 1 million: 36.2%

Serum HBV DNA level and liver disease progression and survival

REVEAL-HBV: summary

• HBV viral load is a strong risk predictor for cirrhosis and HCC independent of HBeAg status, ALT level and other risk factors.

• Baseline serum HBV DNA level > 10,000 copies/mL may start to increase risk of cirrhosis and HCC in HBV carriers aged 30-65 years after > 10 years of follow-up.

• Patients with persistently high HBV DNA level have the highest risk.

• Measurements of HBV viral load may help define which HBV carriers aged 30 years or older are at high risk for cirrhosis and HCC.
Outline

• HBV natural history cohorts
  – REVEAL-HBV
  – SEARCH-B
  – ERADICATE-B

• Risk calculator update

• Conclusions
Flow of SEARCH-B cohort

1278 HBeAg-positive HBV carriers enrolled from 1985 to 2004

- 599 excluded (without achieving HBeAg seroconversion before 2004)
- 189 excluded (treatment-related HBeAg seroconversion)*

490 spontaneous HBeAg seroconverters

- 36 excluded (development of liver cirrhosis (N=33) or HCC (N=3) before HBeAg seroconversion)
- 19 excluded (HBeAg seroreversion)
- 26 excluded (HBeAg-negative hepatitis within 1 year after HBeAg seroconversion)
- 7 excluded (irregular follow-up)
- 12 excluded (inadequate serum for analysis)

409 sustained spontaneous HBeAg seroconverters without meeting the defined endpoints

390 spontaneous HBeAg seroconverters with adequate serum and regular follow-up

Tseng TC, Liu CJ, Kao JH et al. Gastroenterology 2011;141:517-525
Pilot study of viral kinetics in 42 patients

Endpoints of follow-up

- Censored at
  - Meeting each endpoints
  - End of follow-up
  - Starting anti-viral therapy

Definition of endpoints

- **HBeAg-negative hepatitis (ENH)**
  - ALT > 80 U/L (two times the upper limit of normal)
  - HBV-DNA level >2000 IU/ml within 6 months

- **Hepatitis flare**
  - ALT elevation > 5 X ULN with a concomitant serum HBV DNA level > 2000 IU/mL

- **Cirrhosis**
  - Histologically
  - Ultrasonographic findings supplemented with clinical features

- **HCC**
  - Histology/cytology or by typical image findings in hepatic nodules > 1 cm
Prediction of HBsAg loss: HBV DNA vs. HBsAg

Higher HBsAg level predicts incidence of ENH, but not cirrhosis, and HCC


Kao 2015
Higher HBV DNA level predicts more ENH and hepatitis flare

HBeAg(-) hepatitis

Hepatitis flare

@ HBeAg seroconversion may not always confer favorable outcomes. Serum HBV DNA levels > 2000 IU/mL at 1 year post HBeAg seroconversion correlate with increased risk of HBeAg-negative hepatitis and hepatitis flare

Tseng and Kao et al. JID 2012;205: 54-63
SEARCH-B: summary

• In spontaneous HBeAg seroconverters with HBV genotype B or C infection, a lower serum HBsAg level at early HBeAg-negative phase is associated a higher HBsAg loss rate

• HBsAg level <100 IU/mL predicts HBsAg loss within 6 years in spontaneous HBeAg seroconverters with HBV DNA level  200 IU/mL

• Serum HBV DNA level is better than HBsAg level in predicting disease progression in spontaneous HBeAg seroconverters

Tseng and Kao et al. JID 2012;205: 54-63
SEARCH-B: issues remained

• Predictive value
  – For HBsAg loss: HBsAg level is better
  – For adverse outcomes: HBV-DNA level is better

• Explanation
  – HBV-DNA level, compared to HBsAg level, varies within a short period time
  – HBsAg level may be a better marker for immune control of HBV

• Future studies in natural history
  – Predictive value of other biomarkers (e.g. viral variants)
  – Cutoff HBsAg level to define true inactive carriers
  – Role of HBsAg in stratifying risk of disease progression in patients with different viral loads
Flow of SEARCH-B subcohort
qBCPm and cirrhosis risk

490 spontaneous HBeAg seroconverters

36 excluded (development of liver cirrhosis (N=33) or HCC (N=3) before HBeAg seroconversion)

19 excluded (HBeAg seroreversion)

409 sustained spontaneous HBeAg seroconverters without meeting the defined endpoints

26 excluded (HBeAg-negative hepatitis within 1 year after HBeAg seroconversion)

7 excluded (irregular follow-up)

390 spontaneous HBeAg seroconverters with adequate serum and regular follow-up

12 excluded (inadequate serum for analysis)

251 spontaneous HBeAg seroconverters with HBV DNA >200 IU/mL

Methods

• PC and BCP variations
  – Qualitative analysis by Taqman assay (major sequence): in VL >200 IU/mL
  – Quantitative analysis by **pyrosequencing**: in VL >2000 IU/mL

• Statistical analysis
  – Kaplan-Meier failure estimate
  – Cox proportional hazards regression models

1 Yang et al. Hepatology 2013; 57: 934-43

Higher BCP mutant proportion has a higher cirrhosis risk in 151 patients with HBV DNA level > 2000 IU/mL

Categorized by 10% & 90%

<table>
<thead>
<tr>
<th>BCP mutant (%)</th>
<th>Crude hazard ratio for cirrhosis (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>Reference</td>
</tr>
<tr>
<td>10-90</td>
<td>3.55 (1.06-11.85)</td>
</tr>
<tr>
<td>&gt;90</td>
<td>7.68 (2.53-23.37)</td>
</tr>
</tbody>
</table>

Categorized by 45%

Percentage of mutant of basal core promoter (A1762T)
- Mutant < 45%
- Mutant ≥ 45%

Logrank $P < .001$

SEARCH-B subcohort: summary

• PC/BCP variants are not associated with ENH

• A higher proportion of BCP mutant is associated with a higher risk of cirrhosis in patients with HBV DNA level > 2000 IU/mL (high viral load)

Outline

• HBV natural history cohorts
  – REVEAL-HBV
  – SEARCH-B
  – ERADICATE-B

• Risk calculator update

• Conclusions
Flow of ERADICATE-B

- 2688 Taiwanese chronic hepatitis B patients followed for a mean of 14.7 years; cirrhosis excluded by USG

Tseng, Kao et al. Gastroenterology 2012
**ERADICATE-B Study: risk factors for higher HCC risk**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Patients, n</th>
<th>Patient-years of follow-up</th>
<th>HCC, n</th>
<th>Annual incidence rate (per 100,000 patient-years)</th>
<th>Crude HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1054</td>
<td>15,440.3</td>
<td>37</td>
<td>239.6</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>1634</td>
<td>23,986.8</td>
<td>154</td>
<td>642.0</td>
<td>2.7 (1.9–3.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28–39</td>
<td>1407</td>
<td>21,236.5</td>
<td>62</td>
<td>292.0</td>
<td>1.0</td>
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<tr>
<td>40–49</td>
<td>763</td>
<td>11,152.4</td>
<td>54</td>
<td>484.2</td>
<td>1.7 (1.2–2.5)</td>
<td>.004</td>
</tr>
<tr>
<td>50–59</td>
<td>369</td>
<td>5164.7</td>
<td>43</td>
<td>832.6</td>
<td>3.0 (2.1–4.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥60</td>
<td>149</td>
<td>1873.5</td>
<td>32</td>
<td>1708.0</td>
<td>6.9 (4.5–10.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Serum ALT level, U/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>1051</td>
<td>16,611.0</td>
<td>27</td>
<td>162.5</td>
<td>1.0</td>
<td>&lt;.001</td>
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<tr>
<td>20–39</td>
<td>854</td>
<td>11,908.6</td>
<td>49</td>
<td>411.5</td>
<td>2.8 (1.8–4.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥40</td>
<td>783</td>
<td>10,907.6</td>
<td>115</td>
<td>1054.3</td>
<td>7.2 (4.7–511.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HBsAg status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>2165</td>
<td>31,588.6</td>
<td>127</td>
<td>402.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>523</td>
<td>7838.6</td>
<td>64</td>
<td>816.5</td>
<td>2.0 (1.5–2.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Serum HBV DNA level, IU/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>438</td>
<td>6454.6</td>
<td>12</td>
<td>185.9</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>200–1999</td>
<td>649</td>
<td>9780.3</td>
<td>17</td>
<td>173.8</td>
<td>0.9 (0.4–1.9)</td>
<td>.824</td>
</tr>
<tr>
<td>2000–19,999</td>
<td>555</td>
<td>8141.4</td>
<td>30</td>
<td>368.5</td>
<td>2.0 (1.0–3.9)</td>
<td>.044</td>
</tr>
<tr>
<td>20,000–199,999</td>
<td>292</td>
<td>4223.6</td>
<td>32</td>
<td>757.6</td>
<td>4.1 (2.1–8.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥200,000</td>
<td>754</td>
<td>10,827.1</td>
<td>100</td>
<td>923.6</td>
<td>5.1 (2.9–9.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Serum HBsAg level, IU/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>129</td>
<td>1735.8</td>
<td>3</td>
<td>172.8</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>10–99</td>
<td>268</td>
<td>3916.0</td>
<td>8</td>
<td>204.3</td>
<td>1.1 (0.3–4.2)</td>
<td>.881</td>
</tr>
<tr>
<td>100–999</td>
<td>703</td>
<td>10,269.6</td>
<td>43</td>
<td>418.7</td>
<td>2.3 (0.7–7.3)</td>
<td>.171</td>
</tr>
<tr>
<td>1000–9999</td>
<td>1215</td>
<td>18,077.3</td>
<td>108</td>
<td>597.4</td>
<td>3.2 (1.0–10.0)</td>
<td>.048</td>
</tr>
<tr>
<td>≥10,000</td>
<td>373</td>
<td>5428.5</td>
<td>29</td>
<td>534.2</td>
<td>2.9 (0.9–9.5)</td>
<td>.080</td>
</tr>
</tbody>
</table>

| Genotype C |            |                             |        |                                                  |                   |         |
| B          | 1308        | 19,154.7                    | 93     | 485.5                                            | 1.0               | <.001   |
| C          | 312         | 4327.1                      | 69     | 1594.6                                           | 3.4 (2.5–4.6)     | <.001   |

Tseng, Kao. Gastroenterology 2012
ERADICATE-B: HCC according to baseline HBsAg level

- In overall assessment, HBsAg level was not a significant risk factor for HCC
- However, in patients with lower HBV DNA levels, HBsAg level was a significant factor for HCC risk

Clinical utility of HBsAg level in patients with low HBV DNA
HBsAg level is an important risk factor in patients with low HBV DNA level (<2000 IU/mL)

ERADICATE-B (2688 HBV carriers)

<table>
<thead>
<tr>
<th>HBV DNA Level</th>
<th>Risk of HCC (per 100,000 person-year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA ≥ 200000 IU/ml</td>
<td>0.92%</td>
</tr>
<tr>
<td>HBV DNA 20000-199999 IU/ml</td>
<td>0.76%</td>
</tr>
<tr>
<td>HBV DNA 2000-19999 IU/ml</td>
<td>0.37%</td>
</tr>
<tr>
<td>HBV DNA 200-1999 IU/ml</td>
<td>0.17%</td>
</tr>
<tr>
<td>HBV DNA &lt;200 IU/ml</td>
<td>0.19%</td>
</tr>
</tbody>
</table>

HBV DNA <2000 IU/ml and HBsAg ≥1000 IU/ml: 0.33%
HBV DNA <2000 IU/ml and HBsAg <1000 IU/ml: 0.06%

*Start antiviral therapy at annual HCC risk of 0.3%

Tseng, Kao. Gastroenterology 2012; Chan HL. Gastroenterology 2012
**ERADICATE-B subcohort:**

**Low Viremia (LV) cohort**

- 2688 patients without treatment during the follow-up (ERADICATE-B cohort)

- 2165 HBeAg-negative patients

- 523 HBeAg-positive patients

Stratified by their baseline HBV DNA levels

- HBV DNA level: <2000 IU/mL
  - N=1068

- HBV DNA level: 2000-19,999 IU/mL
  - N=521

- HBV DNA level: 20,000-199,999 IU/mL
  - N=248

- HBV DNA level: ≥200,000 IU/mL
  - N=328

HBsAg level > 1000 IU/mL predicts hepatitis flare and cirrhosis

Hepatitis flare

Cirrhosis


Kao 2015
Incidence rates of ENH and HCC in different clinical settings of \textbf{1,068} patients with HBV DNA level <2,000 IU/mL


\begin{tabular}{lccc}
\hline
 & ENH &  & HCC \\
Incidence rate of HBeAg-negative hepatitis per 100 person-years & 2.0 (1.8-2.3) & 1.4 (1.2-1.7) & 1.1 (0.9-1.4) \\
Incidence rate of hepatocellular carcinoma per 1000 person-years & 1.8 (1.3-2.6) & 1.0 (0.8-1.7) & 0.3 (0.1-1.1) \\
\hline
\end{tabular}

\begin{tabular}{lcccc}
\hline
Patient number & 1068 & 910 & 495 & 1068 & 910 & 495 \\
HBV DNA & <2000 IU/mL & \bullet & \bullet & \bullet & \bullet & \bullet \\
ALT & <40 U/L & \bullet & \bullet & \bullet & \bullet & \bullet \\
HBsAg & <1000 IU/mL & \bullet & \bullet & \bullet & \bullet & \bullet \\
\hline
\end{tabular}

Algorithm to categorize disease progression in Asian HBV carriers

Patients
- HBeAg-positive HBV carriers and HBeAg-negative HBV carriers with more than one high viral risk factor from Table 1

Risk level
- High

Follow-up interval or management
- 3 months or start treatment

Abnormal
- Intermediate

Follow-up interval or management
- 3–6 months

ALT level
- Low

Follow-up interval or management
- 6–12 months

Normal
- Minimal

Follow-up interval or management
- 12 months

HBsAg level
- < 1000 IU/mL

Follow-up interval or management
- 12 months

HBsAg-negative HBV carriers with HBV-DNA < 2000 IU/mL

Modified from Tseng et al. Hepatology 2013

Lin & Kao. J Gastroenterol Hepatol 2012
Outline

• HBV natural history cohorts
  – REVEAL-HBV
  – SEARCH-B
  – ERADICATE-B

• Risk calculator update

• Conclusions
**REACH-B risk score**

### Development
- Community-based REVEAL-HBV cohort
  - 23820 cohort members recruited in Taiwan
  - 4155 HBsAg seropositive
  - 3851 tested serum HBV DNA on enrollment sample (REVEAL-HBV cohort)
  - 3653 anti-HCV-seronegative subjects
  - 3584 free of liver cirrhosis at study entry (131 developed HCC during follow-up)

### Validation
- Hospital-based composite international cohort
  - CUHK cohort
    - 426 patients (46 HCC cases)
  - Yonsei U cohort
    - 259 patients (25 HCC cases)
  - UHK cohort
    - 820 patients (40 HCC cases)

### Risk scores and predicted HCC risk for external validation
- 1505 CHB patients for validation (111 developed HCC during follow-up)

* All subjects were free of antiviral therapy during follow-up
*Start antiviral therapy at annual HCC risk of 0.3%
Can incorporation of HBsAg levels improve risk model calculations?
Reclassification of HCC risk in 2165 HBeAg(-) patients

Ongoing works on HCC risk calculator

**Development**
Community-based
REVEAL-HBV cohort

3584 HBsAg-seropositive, anti-HCV-seronegative, free of liver cirrhosis at study entry (208 developed HCC during follow-up)

**Validation**
Hospital-based composite international cohort

- **CUHK cohort**
  - 426 patients (46 HCC cases)

- **ERADICATE-B cohort**
  - 2688 patients (191 HCC cases)

**Model derivation**

Two model / score:

- REACH-B + qHBsAg (REACH-B IIa)
- REACH-B + qHBsAg – HBV DNA level (REACH-B IIb)

* All subjects were free of antiviral therapy during follow-up

## Comparison of various versions of REACH-B models/scores

<table>
<thead>
<tr>
<th></th>
<th>REACH-B</th>
<th>REACH-B IIa</th>
<th>REACH-B IIb</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk parameters</strong></td>
<td>Basic predictors+ HBV DNA</td>
<td>Basic predictors+ HBV DNA+ qHBsAg</td>
<td>Basic predictors+ qHBsAg</td>
</tr>
<tr>
<td><strong>Discriminatory capability</strong></td>
<td>Worst</td>
<td>Best</td>
<td>Good</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>Fairly expensive</td>
<td>Priciest</td>
<td>Cheapest</td>
</tr>
<tr>
<td><strong>Potential usage</strong></td>
<td>Should be replaced by new version tools</td>
<td>Used by hepatologists for management of CHB patients</td>
<td>First-line risk prediction tool for GP; community surveys; countries with limited resources</td>
</tr>
</tbody>
</table>

Predicting Hepatitis B Virus (HBV) Surface Antigen Seroclearance in HBV e Antigen–Negative Patients With Chronic Hepatitis B: External Validation of a Scoring System

Jessica Liu,1,a Tai-Chung Tseng,2,a Hwai-I Yang,1,10,11 Mei-Hsuan Lee,3 Richard Batra-Utermann,13 Chin-Lan Jen,1 Sheng-Nan Lu,12 Li-Yu Wang,4 San-Lin You,1 Pei-Jer Chen,5,7 Chien-Jen Chen,1,8 and Jia-Horng Kao5,6,7

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Outline

• HBV natural history cohorts
  – REVEAL-HBV
  – SEARCH-B
  – ERADICATE-B

• Risk calculator update

• Conclusions
Assessment and modification of risk factors for HCC

- Risk stratification of HCC
- Intervention for risk of HCC

Risk modification for HCC:
- Long-term suppression of HBV-DNA
- Reduction of HBsAg levels

Alter outcome:
- Prevention of HCC development
Conclusions: What have we learned from HBV clinical cohorts?

- CHB is a complex disease with various clinical outcomes.
- HBV natural history cohorts help resolve HBV factors affecting liver disease remission or progression.
- Integrating qHBsAg levels into risk calculators can aid classification of patients whose disease will or will not progress.
- Risk modification by antiviral treatment is mandatory and feasible.