**Supplementary table 1. Definition of different HBeAg-negative stages by clinical practice guidelines and the corresponding patient number in discovery and validation cohorts.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | AASLD (2018) | EASL  (2017) | APASL (2015) |
| Inactive CHB  HBV DNA (IU/mL)  ALT  Number of discovery cohort  Number of validation cohort | < 2000  ≤ ULN  824  608 | < 2000  ≤ ULN  909  671 | < 2000  ≤ ULN  909  671 |
| Immune-active CHB  HBV DNA (IU/mL)  ALT  Number of discovery cohort  Number of validation cohort | > 2000  ≥ 2x ULN  175  69 | > 2000  > ULN  311  128 | > 2000  > 2x ULN  129  46 |
| Indeterminate CHB  Number of discovery cohort  Number of validation cohort | 990+(161)  574+(61) | 930  513 | 1112  595 |
| Upper limit of normal ALT  Male  Female | 35 U/L  25 U/L | 40 U/L  40 U/L | 40 U/L  40 U/L |

**NOTE**

( ) Patients with HBV DNA level ≥20,000 IU/mL+ ALT between 1x-2x ULN

CHB, chronic hepatitis B; ALT, alanine transaminase; HBeAg, hepatitis B e antigen; ULN, upper limit of normal; AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; APASL, The Asian Pacific Association for the Study of the Liver.

**Supplementary table 2. HCC risk of discovery cohort stratified by AASLD-defined HBV DNA and ALT levels**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Groups | HBV DNA (IU/mL) | ALT\* | Patient  Num | P-yrs of follow-up | HCC  Num | Annual incidence rate  (per 100 P-yrs) | Crude HR  (95% CI) | *P*-value |
| 0  1  2  3  4  5  6  7 | < 2000  < 2000  < 2000  2000-19,999  2000-19,999  ≧20,000  ≧20,000  ≧2000 | ≤ULN  1-2x ULN  ≧2x ULN  ≤ULN  1-2x ULN  ≤ULN  1-2x ULN  ≧2x ULN | 824  173  61  394  98  264  161  175 | 13404.57  2585.19  923.23  6498.55  1349.57  4417.17  2409.42  2536.93 | 16  12  6  18  9  28  29  26 | 0.12  0.46  0.65  0.28  0.67  0.63  1.20  1.02 | reference  4.07  (1.92-8.64)  5.12  (1.97-13.32)  2.27  (1.16-4.46)  6.69  (2.95-15.20)  5.18  (2.80-9.59)  11.10  (6.02-20.46)  9.50  (5.09-17.72) | < .001  .001  .017  < .001  < .001  < .001  < .001 |

**NOTE.**

\* Upper limit of normal ALT: 35 U/L for males and 25 U/L for females defined by AASLD guideline

Abbreviations: P-yrs, person-years; HR, hazard ratio; CI, confidence interval; ALT, alanine transaminase; ULN, upper limit of normal; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

**Supplementary table 3. Sensitivities, specificities and Youden indexes of different HBcrAg cutoffs in predicting HCC in indeterminate patients from discovery cohort (N=990, 73 developed HCC)**

|  |  |  |  |
| --- | --- | --- | --- |
| HBcrAg level (U/mL) | Sensitivity (%) | Specificity (%) | Youden index † |
| >5000 | 75.34 | 62.49 | 0.3783 |
| >10,000 | 75.34 | 62.81 | 0.3815 |
| >15,000 | 56.16 | 73.50 | 0.2966 |
| >50,000 | 35.62 | 83.75 | 0.1937 |
| >100,000 | 8.22 | 98.80 | 0.0702 |
| >500,000 | 16.44 | 95.75 | 0.1219 |
| >1000,000 | 8.22 | 98.80 | 0.0702 |

**NOTE.**

Abbreviations: HCC, hepatocellular carcinoma; HBcrAg, hepatitis B core-related antigen.

† Youden index = sensitivity + specificity – 1

**Supplementary table 4. The effect of HBcrAg on HCC risk in 1059 HBeAg-negative patients from discovery cohort with and without antiviral therapy during the follow-up period estimated by Cox-PH marginal structural model with inverse probability of treatment weighting**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Regression  coefficient | SE | HR | 95% CI | | *P*-value |
| Sex (male vs. female) | 0.97 | 0.29 | 2.65 | 1.49 | 4.68 | < .001 |
| Age (per year increase) | 0.08 | 0.01 | 1.08 | 1.06 | 1.10 | < .001 |
| Serum ALT level\* (> ULN vs. ≤ ULN) | 0.88 | 0.30 | 2.42 | 1.34 | 4.37 | .004 |
| HBsAg level (≧1000 vs. <1000 IU/mL) | -0.02 | 0.24 | 0.98 | 0.61 | 1.58 | .941 |
| HBV DNA (per log10  IU/mL increase) | 0.08 | 0.10 | 1.08 | 0.89 | 1.32 | .439 |
| HBcrAg level (≧10,000 vs. <10,000 U/mL) | 1.69 | 0.28 | 5.42 | 3.12 | 9.43 | < .001 |

**NOTE.**

\* Upper limit of normal ALT: 35 U/L for males and 25 U/L for females defined by AASLD guideline

Abbreviations: P-yrs, person-years; SE, standard error; HR, hazard ratio; CI, confidence interval; ALT, alanine transaminase; ULN, upper limit of normal; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; HBcrAg, hepatitis B core-related antigen.

**Supplementary table 5. Patient number with HBcrAg levels < 10,000 and ≥10,000 U/mL in each group of the validation cohort**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Group | HBV DNA (IU/mL) | ALT | Patient  number | HBcrAg <10,000 U/mL, N (%) | HBcrAg ≥10,000 U/mL, N (%) |
| 0 | < 2000 | ≤ULN | 608 | 576 (94.7) | 32 (5.3) |
| 1 | < 2000 | 1-2x ULN | 121 | 116 (95.9) | 5 (4.1) |
| 2 | < 2000 | ≧2x ULN | 47 | 39 (83.0) | 8 (17.0) |
| 3 | 2000-19,999 | ≤ULN | 230 | 204 (88.7) | 26 (11.3) |
| 4 | 2000-19,999 | 1-2x ULN | 59 | 51 (86.4) | 8 (13.6) |
| 5 | ≧20,000 | ≤ULN | 117 | 71 (60.7) | 46 (39.3) |
| 6 | ≧20,000 | 1-2x ULN | 61 | 27 (44.3) | 34 (55.7) |
| 7 | ≧2000 | ≧2x ULN | 69 | 24 (34.8) | 45 (65.2) |

**NOTE.**

\* Upper limit of normal ALT: 35 U/L for males and 25 U/L for females defined by AASLD guideline

Abbreviations: ALT, alanine transaminase; ULN, upper limit of normal; HBV, hepatitis B virus; HBcrAg, hepatitis B core-related antigen.

**Supplementary table 6. Sensitivities, specificities and Youden indexes of different HBcrAg cutoffs in predicting HCC in indeterminate patients from validation cohort (N=574, 15 developed HCC)**

|  |  |  |  |
| --- | --- | --- | --- |
| **HBcrAg level (U/mL)** | **Sensitivity (%)** | **Specificity (%)** | **Youden index †** |
| >5000 | 66.7 | 78.9 | 0.461 |
| >10,000 | 66.7 | 85.2 | 0.519 |
| >15,000 | 60.0 | 88.0 | 0.480 |
| >50,000 | 46.7 | 94.1 | 0.408 |
| >100,000 | 33.3 | 95.3 | 0.286 |
| >500,000 | 6.7 | 96.1 | 0.049 |
| >1000,000 | 0.0 | 98.6 | -0.014 |

**NOTE.**

Abbreviations: HCC, hepatocellular carcinoma; HBcrAg, hepatitis B core-related antigen.

† Youden index = sensitivity + specificity -1

**Supplementary Table 7. HCC risk stratified by serum levels of HBV DNA, ALT, and HBcrAg in HBeAg-negative patients**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | |  | |  |  | |  | | Discovery cohort (N=2150) | | |  | Validation cohort (N=1312) | | |
| Group | HBV DNA (IU/mL) | | ALT\* | | | HBcrAg  (U/mL) | | Num | Annual incidence rate (95% CI)\*\* | Crude HR  (95% CI) | Adjusted HR\*\*\*  (95% CI) | Num | Annual incidence rate (95% CI)\*\* | Crude HR  (95% CI) | Adjusted HR\*\*\*  (95% CI) |
| I | <2000 | | ≤ULN | | |  | | 824 | 0.12  (0.07-0.20) | 1.0 | 1.0 | 608 | 0.073  (0.069-0.077) | 1.0 | 1.0 |
| II | Indeterminate | | | | | <10,000 | | 594 | 0.19  (0.12-0.31) | 1.61  (0.82-3.16) | 1.32  (0.67-2.59) | 481 | 0.085  (0.080-0.091) | 1.16  (0.34-4.00) | 1.35  (0.39-4.71) |
| III | Indeterminate | | | | | ≧10,000 | | 396 | 0.86  (0.66-1.12) | 7.11§  (4.07-12.43) | 6.67§  (3.81-11.68) | 93 | 0.74  (0.65-0.87) | 9.80§  (3.34-28.78) | 14.30§  (4.65-43.93) |
| IV | ≧20,000  2000-19,999 | | >ULN  ≧2x ULN | | |  | | 336 | 1.11  (0.85-1.45) | 10.22§  (5.85-17.85) | 8.02§  (4.59-14.04) | 130 | 0.75  (0.67-0.86) | 10.00§  (3.56-28.12) | 11.65§  (4.01-33.85) |

**NOTE.**

\* Upper limit of normal ALT: 35 U/L for males and 25 U/L for females defined by AASLD guideline

\*\* per 100 person-years

\*\*\*Adjusted by age and sex

† *P* < .05, ‡ *P* < .01, § *P* < .001.

Abbreviations: P-yrs, person-years; HR, hazard ratio; CI, confidence interval; ALT, alanine transaminase; ULN, upper limit of normal; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HBcrAg, hepatitis B core-related antigen.