**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≤ ULN824608 | < 2000≤ ULN909671 | < 2000≤ ULN909671 |
| Immune-active CHB  HBV DNA (IU/mL) ALT  Number of discovery cohort  Number of validation cohort | > 2000≥ 2x ULN17569 | > 2000> ULN311128 | > 2000> 2x ULN12946 |
| 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/L25 U/L | 40 U/L40 U/L | 40 U/L40 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\* | PatientNum | P-yrs of follow-up | HCCNum | Annual incidence rate(per 100 P-yrs) | Crude HR(95% CI) | *P*-value |
| 01234567 | < 2000< 2000< 20002000-19,9992000-19,999≧20,000≧20,000≧2000 | ≤ULN1-2x ULN≧2x ULN≤ULN1-2x ULN≤ULN1-2x ULN≧2x ULN | 8241736139498264161175 | 13404.572585.19923.236498.551349.574417.172409.422536.93 | 16126189282926 | 0.120.460.650.280.670.631.201.02 | reference4.07 (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**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Regressioncoefficient | 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 | Patientnumber | 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 | ≧20,0002000-19,999 | >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.