HCC risk prediction – what's new?

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Professor, Institute of Digestive Disease
The Chinese University of Hong Kong
Disclosures

- Advisory committee member: Gilead
- Speaker: AbbVie, Bristol-Myers Squibb, Echosens & Furui, Gilead, Janssen, Roche
HCC – top killer in areas endemic with hepatitis B virus (HBV)

- >250 million people chronically infected with HBV worldwide
  - 80% in Asian-Pacific regions
- >350,000 new cases of HBV-related HCC annually
- >50% are too advanced for curative treatments
- >200,000 deaths every year

http://www.cancerresearchuk.org/cancer-info/cancerstats/types/liver/incidence/
Early diagnosis of HCC improves survival

HCC surveillance: ultrasound scan + alpha-fetoprotein every 6 months


Surveillance group:

- Smaller HCC (4.2 cm vs. 7.7 cm; p<0.001)
- Fewer HCC (2.6 vs. 3.8, p=0.03)
- Longer survival (88 vs. 26 weeks; p<0.001)

However, 37.6% still died in 5 years

WHO Targets for reducing new cases of and deaths from chronic viral hepatitis

Majority of deaths are related to HCC
IDENTIFY PATIENTS AT RISK
HCC RISK SCORES
Risk factors for HBV-related HCC

- Presence of hepatic inflammation / fibrosis
- High HBV DNA
- Positive HBeAg
- HBV/HCV/HIV coinfections
- HBV Genotype (Genotype C > B in Asians), PC/BCP mutations
- Old Age
- Alcohol consumption
- Family History
- Gender (M > F)
- Obesity, DM, steatosis
- Presence of hepatic inflammation / fibrosis

Good HCC prediction model

- Simple, objective (clearly defined) variables
- Not fixed, but modifiable variables
- Validated in various cohorts
- Acceptable to both academic and non-academic (private) hospital
- Easily applied in real practice
HCC risk scores for HBV-related HCC

CUHK cohort (CU-HCC)
- Hospital clinic
- Training cohort: 1005
- Validation cohort: 424
- FU 10 years; 150 HCC

REVEAL-HBV cohort
- Community non-cirrhotic patients
- Training cohort: 2435
- Validation cohort: 1218
- FU 11 years; 164 HCC

HKU cohort (GAG-HCC)
- Hospital clinic
- Cohort: 820
- Leave-one-out cross-validation
- FU 6 years; 40 HCC

Yuen et al. J Hepatol 2009;50:80
Yang et al. J Clin Oncol 2010;28:2437
Factors in the HCC risk scores

CUHK cohort (CU-HCC)
- Age, albumin, bilirubin, HBV DNA, cirrhosis

HKU cohort (GAG-HCC)
- Male gender, age, HBV DNA, cirrhosis
  (core promoter mutations)

REVEAL-HBV cohort
- Male gender, age, family history, alcohol, ALT, HBeAg, HBV DNA
  Only applicable to non-cirrhotic patients

Yuen et al. J Hepatol 2009;50:80
Wong et al. J Clin Oncol 2010;28:1660
Yang et al. J Clin Oncol 2010;28:2437
## CU-HCC prediction scores

<table>
<thead>
<tr>
<th>Category</th>
<th>Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt;50</td>
<td>+3</td>
</tr>
<tr>
<td></td>
<td>≤50</td>
<td>0</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>≤35</td>
<td>+20</td>
</tr>
<tr>
<td></td>
<td>&gt;35</td>
<td>0</td>
</tr>
<tr>
<td>Bilirubin (μmol/l)</td>
<td>&gt;18</td>
<td>+1.5</td>
</tr>
<tr>
<td></td>
<td>≤18</td>
<td>0</td>
</tr>
<tr>
<td>HBV DNA (log copies/ml)</td>
<td>≤4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>4–6</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>&gt;6</td>
<td>+4</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Yes</td>
<td>+15</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
</tbody>
</table>

CU-HCC score accurately stratifies patients into 3 levels of cancer risk

<table>
<thead>
<tr>
<th>Risk category</th>
<th>5 years</th>
<th>10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>98.3%</td>
<td>97.1%</td>
</tr>
<tr>
<td>5–19</td>
<td>90.5%</td>
<td>71.0%</td>
</tr>
<tr>
<td>≥20</td>
<td>78.9%</td>
<td>67.7%</td>
</tr>
</tbody>
</table>

Wong et al. J Clin Oncol 2010;28:1660
Antiviral therapy altered the natural history - Entecavir therapy reduces HCC in cirrhotic patients

1,466 entecavir-treated patients vs. 424 untreated patients (historical control)

Hazard ratio 0.55 (95% CI 0.31 – 0.99)

Reduction in CU-HCC score by antiviral therapy is translated into lower risk of HCC

1,531 entecavir-treated patients

Wong GL et al. Gastroenterology 2013;144:933-44.
On-treatment ALT normalization lower HCC risks

Registry study of 21,182 on-treatment (ETV or TDF) subjects in Hong Kong (2005–2016)

<table>
<thead>
<tr>
<th>Cumulative incidence of composite endpoint (%)</th>
<th>AASLD</th>
<th>Local</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative incidence of composite endpoint at 6 years (%) (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT (&lt;1 x ULN)</td>
<td>3.51 (3.06–4.02)</td>
<td>4.42 (4.05–4.83)</td>
</tr>
<tr>
<td>ALT (1–2 x ULN)</td>
<td>5.43 (4.84–6.09)</td>
<td>7.25 (5.74–9.12)</td>
</tr>
<tr>
<td>ALT (≥2 x ULN)</td>
<td>7.08 (5.65–8.85)</td>
<td>5.34 (2.23–12.52)</td>
</tr>
</tbody>
</table>

*Baseline ALT, creatinine, platelet, total bilirubin] (log-transformed), albumin, age, sex, HBeAg, antiviral therapy (initiated by ETV or TDF/both), cirrhosis and diabetes mellitus were adjusted in the Cox regression model.

Liver stiffness and HCC

Chronic hepatitis B (N = 1130)

<table>
<thead>
<tr>
<th>LSM Range</th>
<th>No. at Risk</th>
<th>Cumulative Incidence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSM ≤ 8 kPa</td>
<td>595</td>
<td>0.0</td>
</tr>
<tr>
<td>8 &lt; LSM ≤ 12 kPa</td>
<td>285</td>
<td>0.1</td>
</tr>
<tr>
<td>12 &lt; LSM ≤ 18 kPa</td>
<td>130</td>
<td>0.3</td>
</tr>
<tr>
<td>18 &lt; LSM ≤ 23 kPa</td>
<td>53</td>
<td>0.4</td>
</tr>
<tr>
<td>23 kPa ≤ LSM</td>
<td>67</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Chronic hepatitis C (N = 866)

<table>
<thead>
<tr>
<th>LSM Range</th>
<th>No. at Risk</th>
<th>Cumulative Incidence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSM ≤ 8 kPa</td>
<td>511</td>
<td>0.0</td>
</tr>
<tr>
<td>8 &lt; LSM ≤ 12 kPa</td>
<td>130</td>
<td>0.1</td>
</tr>
<tr>
<td>12 &lt; LSM ≤ 18 kPa</td>
<td>79</td>
<td>0.3</td>
</tr>
<tr>
<td>18 &lt; LSM ≤ 23 kPa</td>
<td>47</td>
<td>0.4</td>
</tr>
<tr>
<td>23 kPa ≤ LSM</td>
<td>87</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Wong GL. Gastroenterol Rep (Oxf) 2013
## Liver stiffness-based optimization of HCC risk score

Liver stiffness measurement replaces clinical cirrhosis

<table>
<thead>
<tr>
<th>Factors</th>
<th>LSM-HCC score</th>
<th>CU-HCC score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>✔ ✔</td>
<td>✔</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Albumin</td>
<td>✔ ✔</td>
<td>✔ ✔ ✔</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>✔ ✔</td>
<td>✔</td>
</tr>
<tr>
<td>Liver stiffness measurement</td>
<td>✔ ✔</td>
<td></td>
</tr>
<tr>
<td>Clinical cirrhosis</td>
<td></td>
<td>✔ ✔ ✔</td>
</tr>
</tbody>
</table>

Liver stiffness-based optimization of HCC risk score

**LSM-HCC score**

N=1555, FU 69 months

LSM-HCC score = LSM, age, albumin, HBV DNA

<table>
<thead>
<tr>
<th></th>
<th>LSM-HCC score</th>
<th>CU-HCC score</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year</td>
<td>AUROC 0.89</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>Sn (%) 100</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Sp (%) 71</td>
<td>75</td>
</tr>
<tr>
<td>5-year</td>
<td>AUROC 0.83</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>Sn (%) 92</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>Sp (%) 71</td>
<td>75</td>
</tr>
</tbody>
</table>

Sn: Sensitivity; Sp: Specificity

Prediction and need for HCC surveillance after first 5 years of ETV/TDF therapy in Caucasian CHB patients of PAGE-B cohort

Hypothesis/Aim/Objective:
To assess predictors and need for HCC surveillance beyond year 5 of ETV/TDF in CHB patients

Methods:
• Patient population: 1427 (73%) of the 1951 adult Caucasians with CHB ± compensated cirrhosis included in the PAGE-B cohort who have completed follow-up >5 years without HCC until year 5
• Age at year 5: 57 ± 13 years, males: 70%, baseline cirrhosis: 26%
• Mean follow-up: 8.1 ± 1.6 (median: 8.3) years from ETV/TDF onset

Conclusions:
HCC after the first 5 years of ETV/TDF therapy seems to develop exclusively in patients older than 50 years, while elastographic reversion of cirrhosis at year 5 does not appear to decrease the HCC risk.

Papatheodoridis GV, et al., Abstract 17
Combining LSM with a serum test?
Enhanced Liver Fibrosis (ELF)

- ELF = 2.278 + 0.851 x ln(HA) + 0.751 x ln(PIIINP) + 0.394 x ln(TIMP-1)

Performance of combined ELF-LSM algorithm

Liver stiffness measurement (LSM)
N = 238

- LSM excludes advanced fibrosis
  N = 100

  Perform ELF score

  - ELF score excludes advanced fibrosis
    N = 4
    Advanced fibrosis excluded
    N = 104

  - ELF score gray zone
    N = 60
    Liver biopsy recommended
    N = 60

  - ELF score confirms advanced fibrosis
    N = 20
    Advanced fibrosis confirmed
    N = 74

- LSM confirms advanced fibrosis
  N = 54

- LSM gray zone
  N = 84

Two-step algorithm of LSM-HCC and ELF score

Liang, et al. (Submitted)

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3 risk levels of HCC after HBsAg seroclearance

- **Highest risk**: Male > 50
- **Intermediate risk**: Male ≤50, Female > 50
- **Lowest (no) risk**: Female ≤50

Application of HCC risk scores in real-life practice

Free online HCC risk calculator

https://www.livercenter.com.hk/

HCC risk calculator
乙肝致癌可致命 風險程度有數計

乙肝型肝炎最大的危險，在於最終會惡化為肝硬化及肝癌。若乙肝患者都知道自己患上肝癌的風險，便能與醫生按時間選擇合適的治療策略。本中心根據往的研究成果，設計肝癌風險計算器，讓市民大衆也能輕易使用。

若你是乙肝患者，為患患上肝癌，並有定期做相關檢查，請依照你的檢查報告，輸入正確的資料。報告愈近期，檢查時間相距愈短，計算結果愈準確。

你的資料僅為計算肝癌風險指數之用，我們不會用作其他用途或披露予任何第三方。

計算結果

按照你提供的數據，你的肝癌風險如下。數據愈近期，將影響計算結果的準確程度，敬請留意。

經計算後，你的肝癌風險指數屬於：高

<table>
<thead>
<tr>
<th>提供數據年份開始計算</th>
<th>累計肝癌風險</th>
</tr>
</thead>
<tbody>
<tr>
<td>5年</td>
<td>21.1%</td>
</tr>
<tr>
<td>10年</td>
<td>32.3%</td>
</tr>
<tr>
<td>15年 (推算)</td>
<td>43.5%</td>
</tr>
</tbody>
</table>

你的肝癌風險指數為高風險，必須小心預防。我們建議你與專科醫生預約，定期進行癌症檢查。

計算結果基於本中心的研究：Clinical Scoring System to Predict Hepatocellular Carcinoma in Chronic Hepatitis B Carriers

你是否曾經：乙肝表面抗原血清檢查

是 □ 否 □ 不知道 □
The Hong Kong Association for the Study of Liver Diseases

# HBsAg level in HCC risk score

**Table 4.** The HBV Viral Load-Free Risk Prediction Model (REACH-B IIb) and Corresponding Risk Scores for Various Risk Predictors

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Regression coefficient</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
<th>Risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Referent</td>
<td></td>
<td>-.</td>
<td>0</td>
</tr>
<tr>
<td>Male</td>
<td>0.91297</td>
<td>2.49 (1.77–3.51)</td>
<td>&lt;.0001</td>
<td>2</td>
</tr>
<tr>
<td>Age, 5-year increment</td>
<td>0.47830</td>
<td>1.61 (1.49–1.74)</td>
<td>&lt;.0001</td>
<td>1</td>
</tr>
<tr>
<td>ALT level, U/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>Referent</td>
<td></td>
<td>-.</td>
<td>0</td>
</tr>
<tr>
<td>15–44</td>
<td>0.55670</td>
<td>1.75 (1.28–2.38)</td>
<td>.0004</td>
<td>1</td>
</tr>
<tr>
<td>≥45</td>
<td>1.12898</td>
<td>3.09 (2.02–4.74)</td>
<td>&lt;.0001</td>
<td>2</td>
</tr>
<tr>
<td>HBeAg/HBsAg level, IU/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative/≤100</td>
<td>Referent</td>
<td></td>
<td>-.</td>
<td>0</td>
</tr>
<tr>
<td>Negative/100–999</td>
<td>0.33663</td>
<td>1.40 (0.86–2.29)</td>
<td>.1796</td>
<td>1</td>
</tr>
<tr>
<td>Negative/≥1000</td>
<td>0.85832</td>
<td>2.36 (1.51–3.69)</td>
<td>.0002</td>
<td>2</td>
</tr>
<tr>
<td>Positive/any</td>
<td>2.23016</td>
<td>9.30 (6.01–14.40)</td>
<td>&lt;.0001</td>
<td>5</td>
</tr>
</tbody>
</table>

Hepatitis B virus core-related antigen (HBcrAg)

HBeAg and HBcAg share a 149-amino-acid sequence identity
The Hong Kong Association for the Study of Liver Diseases

Cocktail of HCC risk prediction – fibrosis and viral markers

Conventional factors: age, gender etc

Fibrosis marker: LSM, ELF or other serum markers

Viral marker: HBV DNA in untreated pts

Viral marker: HBsAg HBcrAg in NA-treated pts