Risk stratification-based surveillance of HCC

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Disclosures

- The Novo Nordisk Foundation (NNF) has awarded me a grant that buys me out of my clinical work 50% of my time
  - The NNF has no other involvement in my research

What is risk-based HCC surveillance?

- Patients with different risks of HCC receive different HCC surveillance regimens
  - Now: Ultrasound every 6 months for all
  - The different regimens can use different screening tests, but don't have to
- Why?
  - Reduction in HCC-related mortality
    - Ultrasound is not sensitive enough
  - Fewer false-positive screening tests
    - Patients at the lowest risk of HCC are very unlikely to benefit from HCC surveillance, and a positive screening test is very likely to be a false-positive one
  - Increased cost-effectiveness
  - Higher participation
- Possible downsides
  - More complicated messaging risks losing patients and clinicians

How?

- “HCC risk score” predicts 5-year risk of HCC
  - Re-computed regularly
- Who? Patients who are reasonably likely to
    - Develop HCC
    - Benefit from an early HCC diagnosis
  - F3 fibrosis or compensated cirrhosis (or transplant-listed)
  - No comorbidity that limits survival too much
    - e.g., active cancer, dialysis, severe COPD, heart failure
- Result → Action
  - Patients with a ‘low’ score receive minimal surveillance (or no surveillance)
  - Patients with a ‘high’ score receive extra-intense surveillance (e.g., aMRI)
  - Patients with an intermediate score are surveilled with ultrasound

The ideal

- MELD score for HCC risk
  - A continuous score (6 to 40 points)
  - Part of the hepatology language
- Patients with the same HCC risk score should have the same risk of HCC
  - Just like patients with the same MELD score should have the same risk of death
  - “Accurate enough” for clinical decision-making
- We may need etiology-specific models
  - PAGE-B
    - ≤ 9 : low risk (no surveillance)
    - 10-17 : intermediate risk (ultrasound surveillance)
    - ≥ 18 : high risk (ultrasound surveillance)

Table 3. Construction of the PAGE-B risk score for prediction of hepatocellular carcinoma in Caucasian chronic hepatitis B patients under entecavir or tenofovir. The score ranges from 0 to 25.

Age (years)	Gender	Platelets (/mm³)
16-29: 0	Female: 0	≥200,000: 0
30-39: 2	Male: 6	100,000-199,999: 6
40-49: 4		<100,000: 9
50-59: 6		
60-69: 8		
≥70: 10		

Malinchoc M, Kamath PS, . . . ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;31:864-871.
Papatheodoridis G, Dalekos G, . . . Lampertico P. PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. J Hepatol 2016;64:800-806.
European Association for the Study of the Liver. EASL clinical practice guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.

Existing risk prediction models

Table 1. Exemplar HCC risk stratification tools.

Score or first author name	Study design	Aetiology	Fibrosis	Variables included	Groups at risk	HCC occurrence
HBV infection						
AASL-HCC score	Retrospective	HBV under entecavir or tenofovir	Cirrhotic and non-cirrhotic	Age, albumin, sex, and cirrhosis	Low (0–5), intermediate (6–19), and high risk (>20)	5-year cumulative HCC incidences were 0%, 4.2%, and 17.6%
APA-B	Retrospective	HBV treatment-naïve starting entecavir	Cirrhotic and non-cirrhotic	Age, platelet counts, and AFP levels after 12 months of treatment	Low (0–5), intermediate (6–9), and high risk (10–15)	The HCC risk was predicted at 2,3,4 and 5-year
CAMD	Retrospective	HBV under entecavir or tenofovir	Cirrhotic and non-cirrhotic	Cirrhosis, age, gender, diabetes	Low (<8), Intermediate (8–13), and high risk (14–19)	In the validation cohort, the 3-year cumulative HCC incidences were 0.72%, 3.35%, and 9.17%, respectively.
CU-HCC	Prospective-retrospective cohort	HBV	Cirrhotic and non-cirrhotic	Age, albumin, bilirubin, HBV DNA, cirrhosis	Low, Intermediate, and high-risk	HCC-free survival at 10 years: Low-risk 100%, Medium-risk 75.1% High-risk 61.7%
FIB-4 (Suh 2015)	Retrospective	HBV	Cirrhotic and non-cirrhotic	AST, ALT, platelet, age	FIB-4 (<1.25) FIB-4 (1.25–<1.7) FIB-4 (1.7–<2.4 FIB-4 (≥2.4)	Compared to individuals with FIB-4 <1.25, those with 1.7 ≤FIB-4 <2.4 had an aHR of 4.57, and those with FIB-4 ≥2.4 an aHR of 21.34
GAG-score	Retrospective	HBV	Cirrhotic and non-cirrhotic	Age, sex, HBV DNA, core promoter mutations, cirrhosis	NA	A diagram was developed to predict the risk at 5 and 10 years
LSM Score	Prospective	HBV	F0–F4	LSM, age, albumin, HBV DNA	Low, intermediate, and high risk	In the validation cohort, 5-year HCC risks were 0.3%, 5%, and 12.3%
PAGE-B*	Retrospective	HBV	Cirrhotic and non-cirrhotic	Age, sex and platelet	Low (≤9), intermediate (10–17), and high risk (>18)	The 5-yr cumulative probability of HCC in low, intermediate, and high risk-groups was 0%, 3% and 17%
Chang	Retrospective	HCV after interferon therapy	Cirrhotic	Age, sex, platelet, AFP, advanced fibrosis, HCV genotype 1b, SVR	Low, intermediate, and high-risk	In the validation cohort, the 5-year HCC incidences were 1.81%, 12.92%, and 29.95% in low-, intermediate-, and high-risk groups
El-Serag	Retrospective	HCV	Cirrhotic	AFP, ALT, platelet, age	N/A	An algorithm was developed to calculate HCC risk
Ganne-Carrié	Prospective-retrospective	HCV	Cirrhotic	Age, past alcohol abuse, platelet, GGT, SVR	Low (≤3), intermediate (4-7), and high risk (≥8)	A nomogram was built to predict HCC risk at 1-, 3- and 5-yrs
Ioannou (RNN)	Retrospective	HCV after antiviral treatment (SVR and non-SVR)	Cirrhotic and non-cirrhotic	Recurrent Neural Network	Four models were developed in patients with or without cirrhosis and with or without SVR	Recurrent Neural Network predicted HCC risk at 3 years
Multi-aetiology						
Fan R (aMAP score)*	Retrospective	Multiple aetiologies	Cirrhotic and non-cirrhotic	Age, gender, bilirubin, albumin, PLT	Low (<50), intermediate (50-60), and high risk (>60)	HCC incidences at 3–5 years were 0–0.8% *vs.* 1.5–4.8% *vs.* 8.1–17.8%
Fujiwara	Prospective-retrospective	All aetiologies	Cirrhotic and non-cirrhotic	PLSec, AFP	Low risk <1.66, High risk ≥1.66	8.8% *vs.* 18.1% at 5 years, 15.2% *vs.* 32.7% at 10 years
Hiraoka A (ADRES score)	Retrospective	Multiple aetiologies	cALD	Gender, SVR24 FIB-4 and SVR24 AFP	ADRES 0-1-2-3	ADRES 0 *vs.* 1 *vs.* 2 *vs.* 3 0% *vs.* 0.5% *vs.* 8.4% *vs.* 18% at 1 year 0% *vs.* 1.6% *vs.* 13.4% *vs.* 32.8% at 2 years
Nahon	Prospective	Alcohol, NAFLD, cured HCV	Cirrhosis	Sex, age, platelet count, bilirubin GGT, AFP	Low risk <9 *vs.* high risk ≥9	Annual HCC incidence >3% in high risk-group
Singal	Prospective-retrospective	Multiple aetiologies	Cirrhotic	23 variables included	A machine learning approach	

Singal AG, Sanduzzi-Zamparelli M, Nahon P, Ronot M, Hoshida Y, Rich N, et al. International Liver Cancer Association (ILCA) white paper on hepatocellular carcinoma risk stratification and surveillance. J Hepatol 2023;79:226-239.

Example 1

- Development: 3,688 Chinese patients with chronic hepatitis B with or with cirrhosis
  - 95 patients developed HCC
  - C-index = 0.82
- Validation in 9 cohorts
  - Different etiologies, different regions
  - C-indices = 0.82 to 0.87

$$\begin{aligned}\text{aMAP risk score} = (\{&0.06 \times \text{age} + 0.89 \times \text{sex (Male: 1, Female: 0)} \\ &+ 0.48 \times [(\log_{10} \text{bilirubin} \times 0.66) \\ &+ (\text{albumin} \times -0.085)] - 0.01 \\ &\times \text{platelets}\} + 7.4) \,/\, 14.77 \times 100,\end{aligned}$$

Fan R, Papatheodoridis G, . . . Hou J. aMAP risk score predicts hepatocellular carcinoma development in patients with chronic hepatitis. J Hepatol 2020;73:1368-1378.

C-index?

- C-index of 0.82 means this:
  - Take all possible pairs of patients and rank them by their HCC risk score
  - 82% of the pairs will be ranked correctly
    - Meaning that the patient with the higher risk score develops HCC first
- C-index = ability to rank patients by their risk of HCC (discrimination)
- C-index ≠ ability to predict the actual risk of HCC (calibration)
- In practice, we choose between models based on their **discrimination**, not their calibration
  - Like the MELD score and the Child-Pugh score

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Example 2

- 836 patients with HCV-related cirrhosis
  - C-P class A, no history of cirrhosis complications
  - “Absence of severe uncontrolled extrahepatic disease resulting in an estimated life expectancy of less than 1 year”
  - 434 patients for a separate model of HCC risk from SVR
  - A narrowly defined cohort!
- Validation cohort: 668 similar patients (46% followed from SVR)

Audureau E, Carrat F, . . . Nahon P. Personalized surveillance for hepatocellular carcinoma in cirrhosis - using machine learning adapted to HCV status. J Hepatol 2020;73:1434-1445.

Table 3. Predictors of HCC occurrence following SVR: results of multivariate competing risk Fine-Gray regression model.

	Univariate analysis		Multivariate analysis		
	SHR (95% CI)	aSHR (95% CI)	aSHR (95% CI)	aSHR (95% CI)	Regression coefficient
Gender, males	0.87 (0.36–2.11)	0.76		-	
Age, years					
Continuous	1.02 (0.99–1.06)	0.19		-	
>60	1.30 (0.53–3.16)	0.57		-	
Past excessive alcohol intake	1.49 (0.63–3.55)	0.37		-	
Tobacco consumption					
Never	1 (ref)			-	
Past	0.86 (0.22–3.36)	0.83		-	
Ongoing	1.34 (0.51–3.48)	0.55		-	
BMI, kg/m^2					
Continuous	1.02 (0.94–1.11)	0.59		-	
Normal weight <25	1 (ref)			-	
Overweight [25–29.9]	1.44 (0.51–4.08)	0.50		-	
Obesity ≥30	0.88 (0.18–4.24)	0.88		-	
Diabetes	1.98 (0.78–5.01)	0.15		-	
Hypertension	1.87 (0.77–4.58)	0.17		-	
HCV genotype 1	0.83 (0.34–2.02)	0.67		-	
Creatinine, µmol/L	0.99 (0.97–1.01)	0.42		-	
eGFR (MDRD)	1.00 (0.99–1.00)	0.39		-	
Serum ferritin, µg/L	1.00 (1.00–1.00)	0.23		-	
Total bilirubin, µmol/	1.01 (0.98–1.04)	0.57		-	
AST, × normal					
Continuous	1.42 (1.08–1.87)	**0.013**	1.27 (0.86–1.89)	0.23	0.239
≥1.5	1.86 (0.73–4.77)	0.19		-	
ALT, × normal					
Continuous	1.28 (0.94–1.75)	0.11		-	
≥2.5	2.11 (0.77–5.83)	0.15		-	
GGT, × normal					
Continuous	1.08 (0.97–1.19)	0.16		-	
>1.5	2.66 (1.00–7.08)	0.051		-	
ALP, × normal					
Continuous	1.53 (1.03–2.27)	**0.037**		-	
>1	2.24 (0.85–5.88)	0.10		-	
Serum albumin, g/L					
Continuous	0.96 (0.90–1.03)	0.26		-	
≤40	1.06 (0.44–2.59)	0.89		-	
Alpha-fetoprotein, ng/ml					
Continuous	0.98 (0.95–1.02)	0.32		-	
≥6	1.65 (0.64–4.24)	0.30		-	
Platelet count, 10^3/µl					
Continuous	0.99 (0.98–1.01)	0.27		-	
<70	4.57 (1.73–12.05)	**0.002**	2.33 (0.77–7.05)	0.13	0.846
Prothrombin time (%)					
Continuous	0.98 (0.96–0.99)	**0.007**		-	
≤85	6.04 (1.97–18.47)	**0.002**	4.30 (1.26–14.70)	**0.02**	1.459

Derivation cohort, n = 434 patients at the time of SVR. Bold values reached statistical significance. ALP, alkaline phosphatase; ALT, alanine aminotransferase; aSHR, adjusted sub-hazard ratio; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; GGT, gamma glutamyltransferase; HCC, hepatocellular carcinoma; SHR, sub-hazard ratio; SVR, sustained virological response.

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Example 2

- HCC risk score =
  0.239 * AST +
  0.846 * Platelets +
  1.459 * Prothrombin time

- C-index ~ 0.62 to 0.70
  - Lower than the aMAP score
  - It is more difficult to reach a high C-index (= rank patients by their HCC risk) within a homogenous cohort
    - Maybe the aMAP score is simply a predictor of having cirrhosis or not
  - We need to compare prediction models in the same cohort

Table 4. Discriminative performance (C-indexes) of each modeling approach.

	Training set	External validation set
Fine-Gray regression model		
Before SVR	0.697	0.645
After SVR	0.807	0.638
Single decision tree by recursive partitioning		
Before SVR	0.652	0.598
After SVR	0.677	0.623
Survival random forest		
Before SVR	0.901/0.633*	0.715
After SVR	0.981/0.741*	0.698

SVR, sustained virological response.
*Apparent C-index/internally validated C-index from out of bag predictions.

Audureau E, Carrat F, . . . Nahon P. Personalized surveillance for hepatocellular carcinoma in cirrhosis - using machine learning adapted to HCV status. J Hepatol 2020;73:1434-1445.

Moving forward

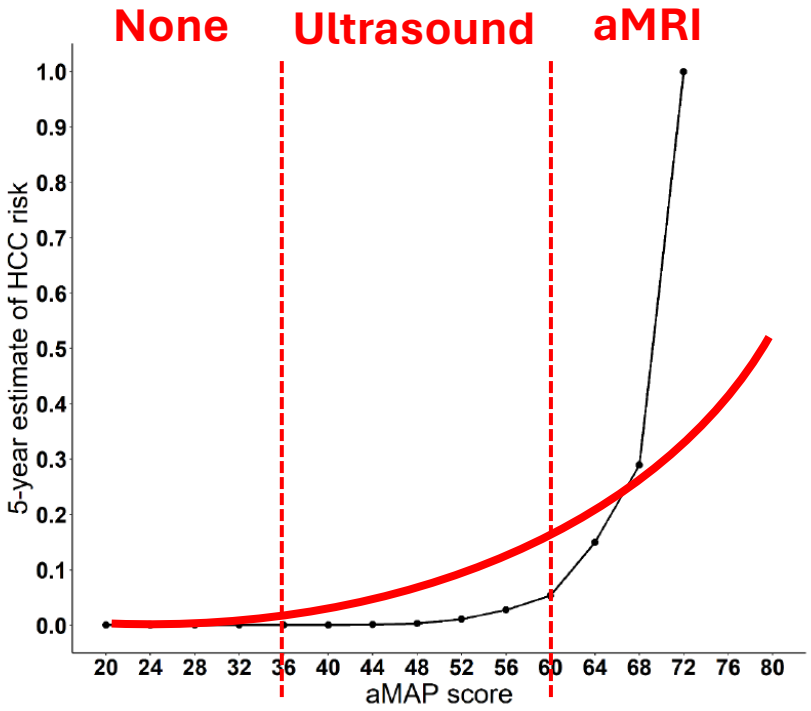
- We have identified must-include variables:
  - Gender, age, indicator(s) of cirrhosis severity/portal hypertension
- Candidates for improved predictions
  - Lifestyle factors?
  - Genetic risk factors?
    - “The incorporation of genetic information modestly improves the performance of clinical scores”
      - aMAP score: C-index from 0.77 to 0.79 by adding genetic risk factors
    - Editorial: “Not yet a game-changer”
  - Risk factors for death without HCC?
    - If you are very likely to die without HCC, you are very unlikely to develop HCC
- Use existing cohorts to compare candidate prediction models
  - Choose the best prediction model

Semmler G, Meyer EL, . . . Mandorfer M. HCC risk stratification after cure of hepatitis c in patients with compensated advanced chronic liver disease. J Hepatol 2022;76:812-821.
Nahon P, Bamba-Funck J, . . . Audureau E. Integrating genetic variants into clinical models for hepatocellular carcinoma risk stratification in cirrhosis. J Hepatol 2023;78:584-595.
Innes H. Genetic data not yet a "game-changer" for predicting individualised hepatocellular carcinoma risk. J Hepatol 2023;78:460-462.
Innes H, Jepsen P, . . . Guha IN. Performance of models to predict hepatocellular carcinoma risk among UK patients with cirrhosis and cured HCV infection. JHEP Rep 2021;3:100384.

Moving forward

- Correlate HCC risk score with observed 5-year risk of HCC across many cohorts
- Design HCC surveillance strategy
  - Formulate thresholds that dictate different HCC surveillance regimens. For example:
    - < 36 : No surveillance
    - 36-60 : Ultrasound surveillance
    - > 60 : aMRI surveillance
  - Re-evaluate (every 1 or 2 years)

Fig. S5. Five-year estimate of hepatocellular carcinoma risk corresponding to the aMAP score.



Fan R, Papatheodoridis G, . . . Hou J. aMAP risk score predicts hepatocellular carcinoma development in patients with chronic hepatitis. J Hepatol 2020;73:1368-1378.
Innes H, Nahon P. Statistical perspectives on using hepatocellular carcinoma risk models to inform surveillance decisions. J Hepatol 2023;79:1332-1337.

Moving forward

- Compare different HCC surveillance strategies in an RCT
  - Randomize patients (or centers) to different strategies
  - Which HCC surveillance strategy has the strongest effect on (HCC-related) mortality?
    - Harms, costs
- Decision-analytic model found that risk-stratified strategies were more cost-effective than ultrasound for all
- Ongoing randomized studies
  - NCT05095714: 1-year risk >3%: ultrasound+fast-MRI vs. ultrasound only
  - NCT05657249: HCC risk score > -2.04: ultrasound 6 months + MRI 1 year

Goossens N, Singal AG, . . . Hoshida Y. Cost-effectiveness of risk score-stratified hepatocellular carcinoma screening in patients with cirrhosis. Clin Transl Gastroenterol 2017;8:e101.
Nahon P, Ronot M, . . . Audureau E. Study protocol for FASTRAK: A randomised controlled trial evaluating the cost impact and effectiveness of fast-MRI for HCC surveillance in patients with high risk of liver cancer. BMJ Open 2024;14:e083701.

Conclusion

- Risk-based HCC surveillance is believed to be superior to the current one-size-fits-all recommendation
- Multiple steps
  - Which predictors go into the prediction model?
    - Gender, age, cirrhosis severity, add-ons
  - Which prediction model is the best?
    - Compare them within existing patient cohorts
  - Propose surveillance strategy based on prediction model
    - PAGE-B, for example
  - How do we know which prediction-based surveillance strategy is best?
    - RCTs, ideally with a mortality outcome
- This is an ongoing effort, and it has already started!

Thank you!