Cairo APASL STC 2022

Risk assessment of HCC development based on noninvasive surrogates

George V. Papatheodoridis

Professor in Medicine & Gastroenterology

Medical School of National & Kapodistrian University of Athens

Director of Academic Gastroenterology Department,
& Liver Transplantation Unit
General Hospital of Athens "Laiko", Greece

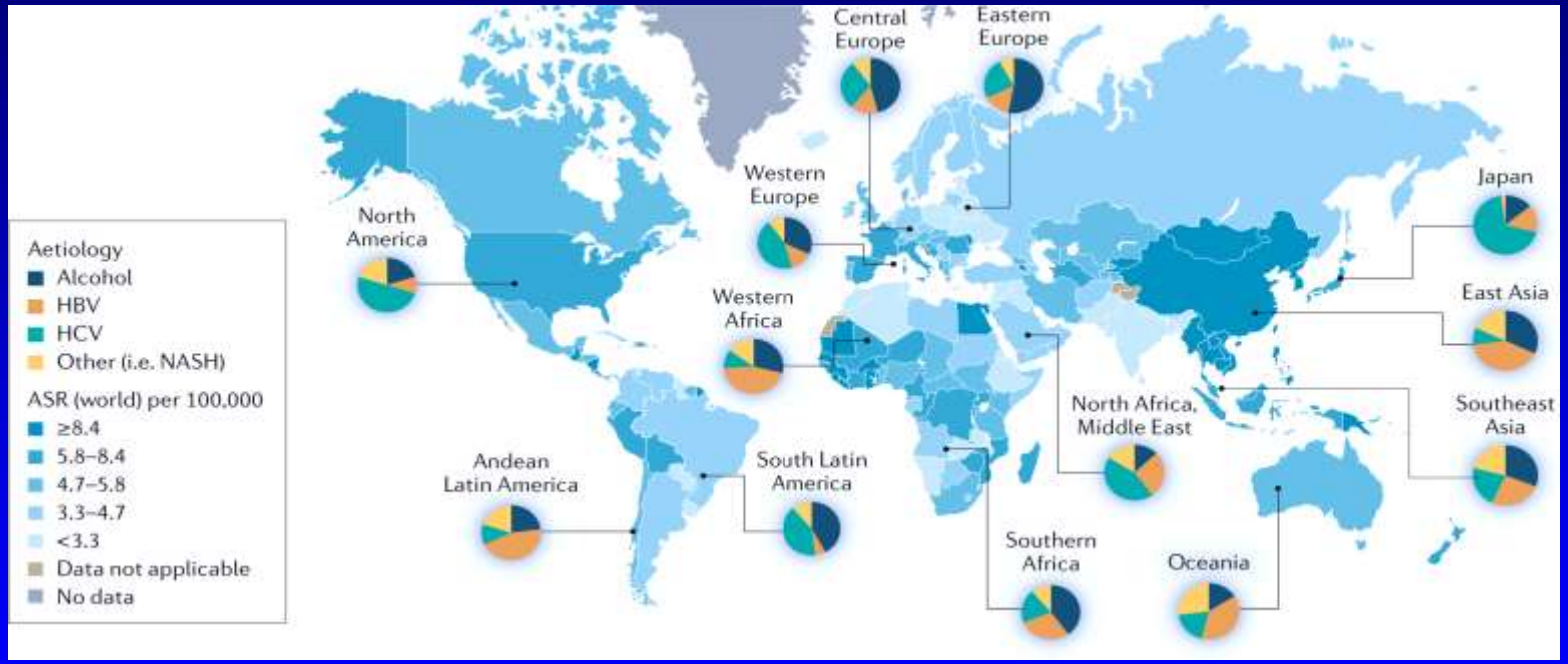
George Papatheodoridis – Disclosure information

- **Advisor/Consultant: Abbvie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Novartis, Roche**
- **Lectures: Abbvie, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Novartis, Roche**
- **Grants: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Roche**
- **Clinical trials: Abbvie, Astellas, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp & Dohme, Noorik, Novartis, Novo Nordisk, Regulus, Roche, Takeda**
- **Data Safety Management Board: Gilead**

HCC epidemiology & Risk factors

~90% of HCCs are associated with a known underlying cause of liver injury

HBV cirrhosis-CHB
The most common factor worldwide



HCV cirrhosis
In developed countries with low HBV endemicity - Rapid decline after DAAs

Alcohol abuse
In developed countries with low HBV/HCV endemicity

Other causes
NASH: rapidly increasing

Incidence of HCC in Risk Groups

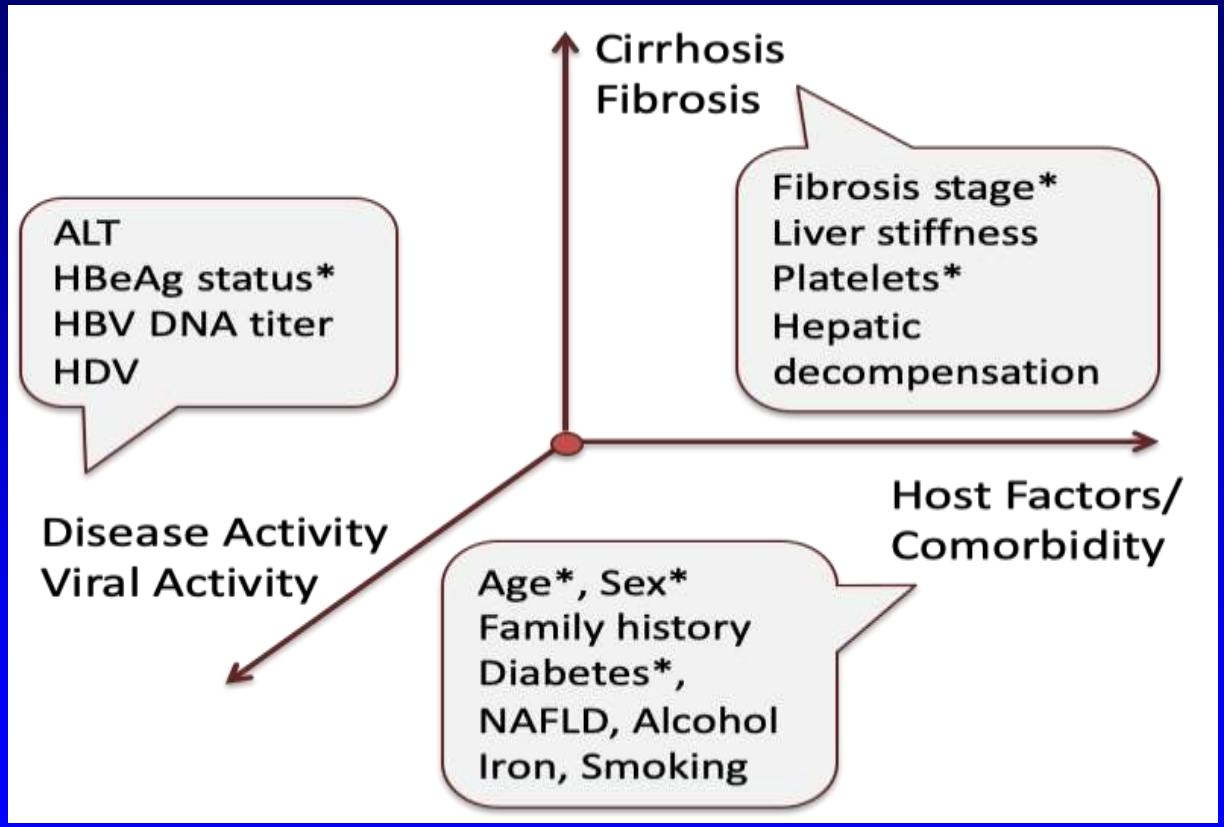
Subgroup	Incidence per Year (%)
All HBV carriers >40 years of age	0.2
HBV cirrhosis	3-8
HCV cirrhosis	3-5
Stage 4 primary biliary cirrhosis	3-5
Alcoholic cirrhosis	?
Genetic hemochromatosis	?
Nonalcoholic steatohepatitis / Cirrhosis	?

Beasley RP et al. Lancet 1981;2:1129-33. Degos F et al. Gut 2000;47:131-6. Caballeria L, et al. Am J Gastroenterol 2001;96:1160-3. Fattovich G. J Hepatol 2003;39 (Suppl 1):S50-8. Manno M et al. Gastroenterology 2004;127:756-63.

Risk factors for HCC in chronic HBV patients

HBV therapy

- IFNa or NA
- Type of NA
- Duration of NA
- Liver stiffness during therapy
- HBsAg loss



Comedications

- Statins
- Antiplatelets

Papatheodoridis GV, Voulgaris T, Papatheodoridi M, Kim WR. Hepatology 2020;72:2197-205.

When HCC surveillance is not recommended

Recommendations are based on decision analyses, cost-effectiveness models & expert opinions

HCC surveillance is not recommended in

- **Child C cirrhosis, except for patients on transplant list**
- **Cirrhotics with an annual HCC risk of <1.5%**
- **Non-cirrhotics with an annual HCC risk of <0.2%**

No age limit

EASL–EORTC CPGs. J Hepatol 2018;69:182-236.

Risk assessment of HCC development based on noninvasive surrogates

- **Non-invasive biomarkers of liver fibrosis severity**
- **HCC risk scores**
- **Emerging approaches**
  - ***Recent non-invasive biomarkers of HCC***
  - ***Prognostic models of HCC***

Liver elastography

Transient (Fibroscan®)

Shearwave

COMBINED EPIDEMIO-SEROLOGICAL MARKERS OF FIBROSIS

- **Fibrotest®** (α_2-macroglobulin, GGT, apolipoprotein A_1, haptoglobin, bilirubin, age, sex)
- **Forns index** (age, PLT, cholesterol, GGT)
- **APRI** (AST, PLT)
- **Lok's index** (PLT, AST/ALT, INR)
- **FibroSpect®** (α_2-macroglobulin, hyaluronic acid, TIMP-1)
- **Enhanced liver fibrosis score** (age, alcohol use, cholesterol, HOMA-IR)
- **GUCI** (Goteborg University Cirrhosis Index) (AST, INR, PLT)
- **Hepascore®** (bilirubin, GGT, hyaluronic acid, α_2-macroglobulin, age, sex)
- **Fibrometers®** (PLT, PT, AST, α_2- macroglobulin, hyaluronic acid, urea, age)

COMBINED EPIDEMIO-SEROLOGICAL MARKERS OF FIBROSIS

- **Fibroindex** (PLT, AST, gamma-globulin)
- **Virahep-C model** (AST, PLT, alkaline phosphatase, age)
- **Zeng model** (age, α_2- macroglobulin, hyaluronic acid, GGT)
- **Hui index** (BMI, bilirubin, PLT, albumin)
- **SHASTA index** (hyaluronic acid, AST, albumin)
- **FIB-4 score** (age, AST, ALT, PLT)
- **NAFLD fibrosis score** (age, hyperglycemia, BMI, PLT, albumin, AST/ALT)
- **European Liver Fibrosis (ELF) test** (age, TIMP-1, hyaluronic acid, P3NP)
- **BARD score** (BMI, AST/ALT, type 2 diabetes)

Non-invasive biomarkers of liver fibrosis severity

- Mainly studied for the assessment of liver fibrosis severity and not of HCC risk
- Mostly reliable for diagnosis of cirrhosis, which is strongly associated with the HCC risk
- Some markers (especially liver stiffness by elastography) are included in some HCC risk scores

Risk assessment of HCC development based on noninvasive surrogates

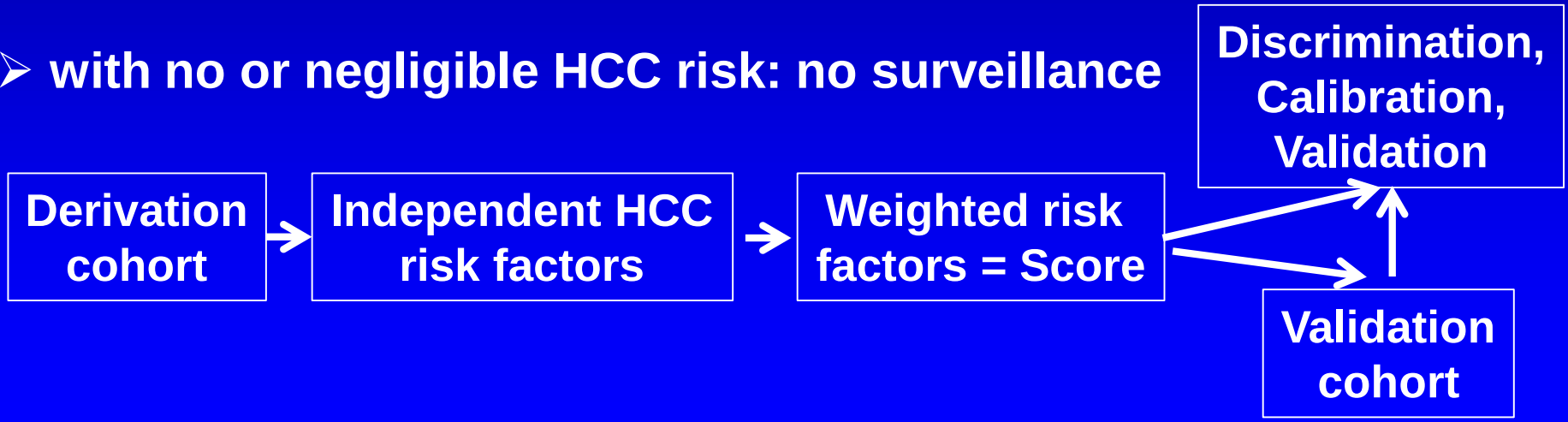
- Non-invasive biomarkers of liver fibrosis severity
- HCC risk scores
- Emerging approaches
  - *Recent non-invasive biomarkers of HCC*
  - *Prognostic models of HCC*

HCC risk scores

Try to differentiate patients according to their HCC risk,

but mainly aim to differentiate patients

- **with at least a minimum HCC risk: surveillance**
- **with no or negligible HCC risk: no surveillance**



Key characteristics of HCC risk scores

1. **Negative predictive value (NPV) of low-risk cut-off[1]**
2. **Simplicity, easy to use in clinical practice**
3. **AUROC**
4. **Proportion of patients in low risk group**

[1]HCC surveillance cost-effective: if annual HCC incidence ≥0.2% in non-cirrhotics & ≥1.5% in cirrhotics

EASL HCC CPGs, 2012/2018

Main HCC risk scores developed in cohorts of untreated CHB patients

Risk score	Country/Area	1st author	Year	Score parameters
GAG-HCC	Hong Kong	Yuen	2009	Age, Sex, HBV DNA, Cirrhosis
CU-HCC	Hong Kong	Wong VW	2010	Age, Alb, Bil, HBV DNA, Cirrhosis
REACH-B	Taiwan /Hong Kong Korea	Yang	2011	Age, Sex, ALT, HBeAg, HBV DNA
REACH-B II	Taiwan	Lee	2013	Age, Sex, ALT, HBeAg, HBV DNA, qHBsAg, genotype, family history
LS Model	Korea	Kim	2013	Age, Sex, HBV DNA, LSM
LSM-HCC	Hong Kong	Wong GL	2014	Age, Albumin, HBV DNA, LSM
LSPS	Korea	Shin	2015	PLT, LSM, Spleen size
RWS-HCC	Singapore	Poh	2016	Age, Sex, Cirrhosis, aFP
AGED	China	Fan	2019	Age, Sex, HBeAg, HBV DNA

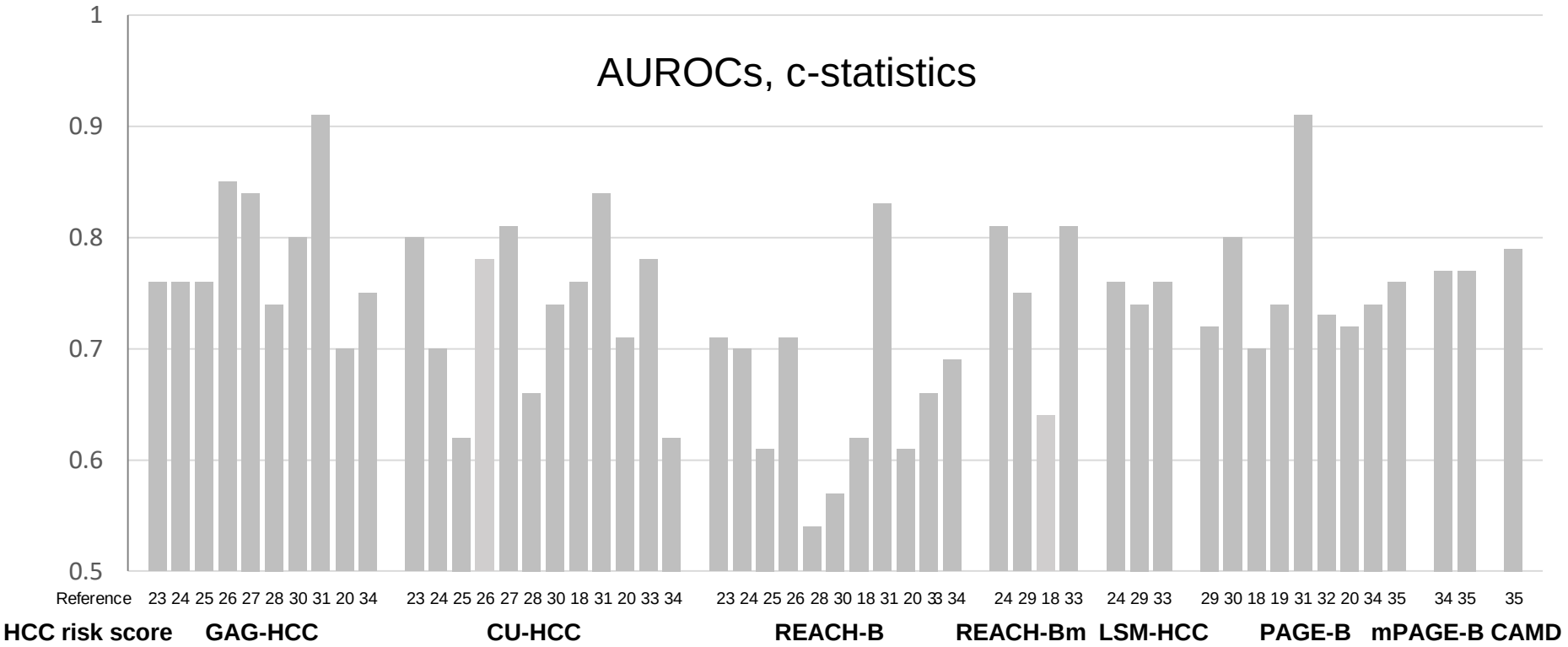
Voulgaris T, Papatheodoridi M, Lampertico P, Papatheodoridis GV. Liver Int 2020;40:484-495.

HCC risk scores developed in cohorts of NA treated CHB patients

Risk score	Country/Area	1st author	Year	Score parameters
REACH-Bm	S Korea	Lee	2014	Age, Sex, LSM , ALT, HBeAg
PAGE-B	Europe	Papatheodoridis	2016	Age, Sex, Platelets
HCC-RESCUE	S Korea	Sohn	2017	Age, Sex, Cirrhosis
APA-B	Taiwan	Chen	2017	Age, Platelets, aFP
CAMD	Taiwan/Hong-Kong	Hsu	2018	Age, Sex, Cirrhosis, Diabetes
mPAGE-B	S Korea	Kim	2018	Age, Sex, Platelets, Albumin
AASL	S Korea	Yu	2019	Age, Sex, Cirrhosis, Albumin

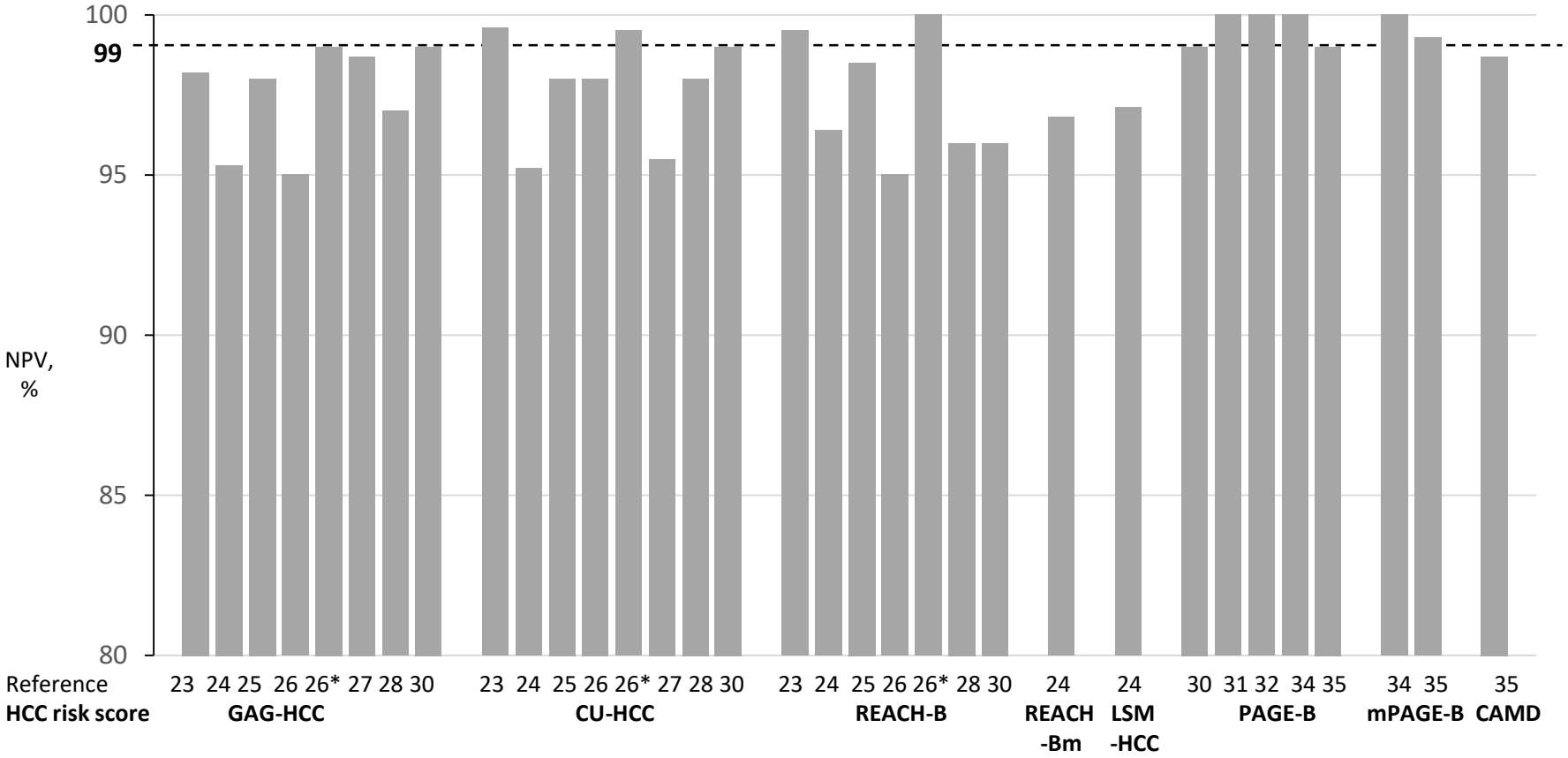
Voulgaris T, Papatheodoridi M, Lampertico P, Papatheodoridis GV. Liver Int 2020;40:484-495.

HCC prediction by several risk scores



Papatheodoridis GV, Voulgaris T, Papatheodoridi M, Kim WR. Hepatology 2020;72:2197-205.

Negative predictive values (NPV) for low-risk groups of several HCC risk scores



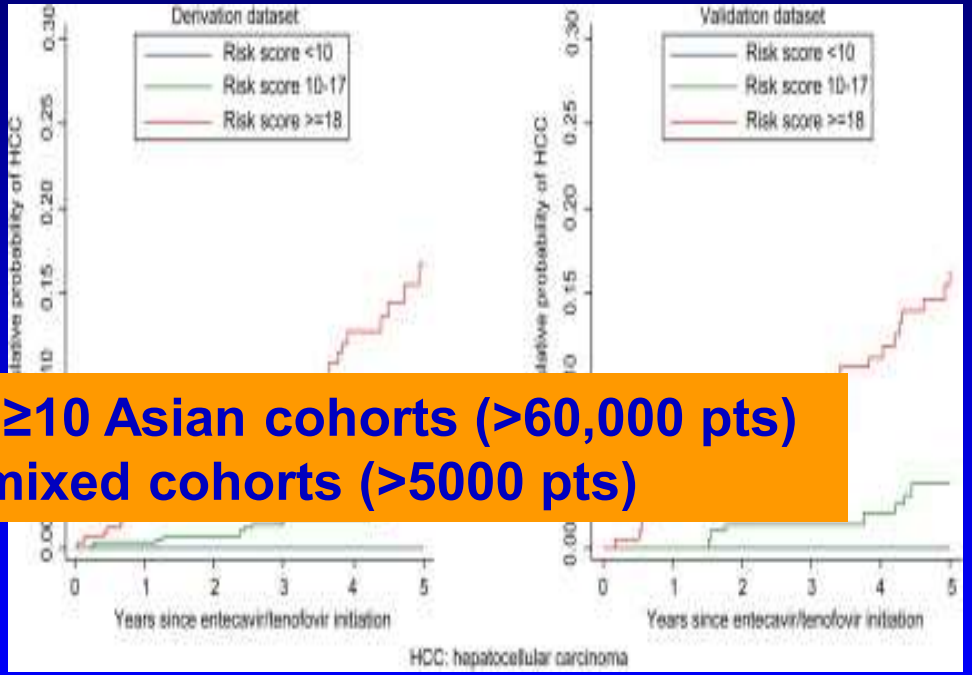
Papatheodoridis GV, Voulgaris T, Papatheodoridi M, Kim WR. Hepatology 2020;72:2197-205.

PAGE-B: a simple to use HCC risk score for the first 5 years of ETV/TDF in Caucasian CHB patients

Recommended for Caucasian CHB patients by EASL HBV & HCC Guidelines

Construction of the PAGE-B risk score for HCC

Age (years)	Gender	Platelets (/mm^3)
16–29: 0	Female: 0	≥200,000: 0
30–39: 2	Male: 6	100,000–199,999: 6
40–4		
50–5		
60–69: 8		
≥70: 10		



Independently validated in ≥10 Asian cohorts (>60,000 pts) & in ≥5 Caucasian/mixed cohorts (>5000 pts)

Males ≥40 yrs, females ≥70 yrs, PLT <200,000/100,00 /mm^3 & age ≥40/30 yrs or males: moderate to high HCC risk

Papatheodoridis GV et al. J Hepatol 2016;64:800-6

Models of HCC risk in HCV patients

➢ **45,810 HCV patients treated with IFNa and/or DAAs based regimens**

HCC risk models

- **No cirrhosis, no SVR/SVR**: sex, age, BMI
- **Cirrhosis, no SVR**: age, BMI, race/ethnicity; **Cirrhosis, SVR**: age, race/ethnicity

GN Ioannou et al. J Hepatol 2018;69:1088-98.

➢ **993 HCV patients with advanced fibrosis and SVR after DAAs**

- **TE-based HCC risk model** - score 0*: 0% HCC occurrence at 3 years
  *baseline LSM ≤17.3 kPa, albumin >4.2 g/dL and 1-yr DeltaLSM >25.5%
- **FIB-4 based HCC risk model** – score 0#: 0.4% HCC occurrence at 3 years
  #baseline FIB-4 ≤3.7, albumin >4.2 g/dL and 1-yr FIB-4 ≤3.3 and 1-yr GGT ≤42 IU/L

S Alonso López et al. Hepatology 2020;72:1924-34.

➢ **836 patients with HCV cirrhosis**

- **Machine learning algorithms** - **non-SVR**: PLT, GGT, AFP, albumin; **SVR**: PT, ALT, age, PLT

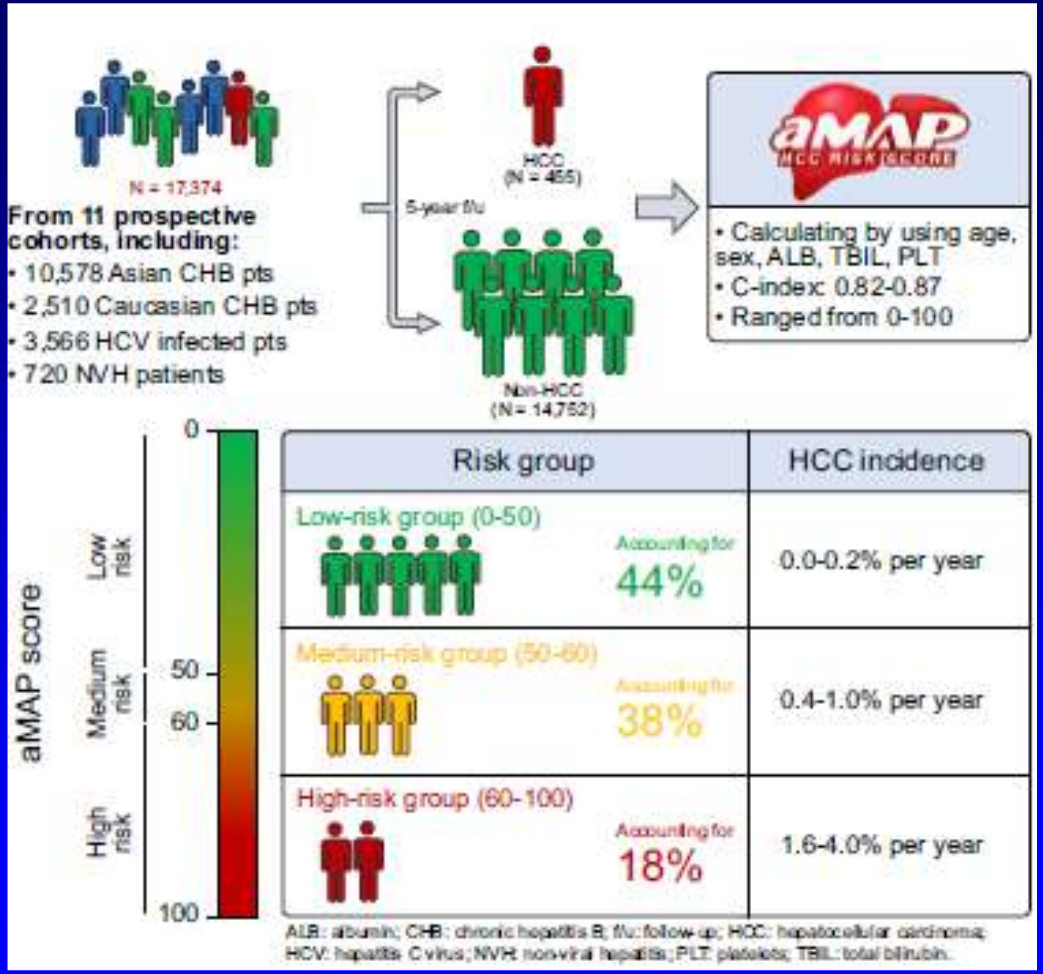
E Audureau et al. J Hepatol 2020;73:1434-45.

17,374 pts
Cirrhosis: 30%
Asians: 71%,
Caucasians: 29%

HBV: 75.3%
HCV: 20.5%
Non-VH: 4.1%

AUROCs: 0.82-0.87

<u>Cut-off: 50</u>
NPV: 99.5%
for 5-year HCC risk prediction



R Fan, G Papatheodoridis, J Sun et al. J Hepatol 2020;73:1368-78.

HCC risk prediction in patients with cirrhosis

34,932 pts
(HCV: 46%
NASH/Crypto: 18%
Alcohol: 18%
PBC: 5%
PSC: 6%

AUROC:
0.69-0.70
for 1-year HCC prediction

TABLE 3. Calculation of 1-Year HCC Risk Using the ADRESS-HCC Model

Step 1: calculate ADRESS-HCC score =
([age] + [*d*iabetes] + [*r*ace] + [*e*tiology] + [*s*ex] + [*s*everity]) in which:
Age indicates the age in years × 0.0532
Diabetes indicates 0.2135 if present and 0 if absent
Race indicates 0.2058 if nonwhite or Hispanic or 0 if non-Hispanic white
Etiology indicates 0 if autoimmune, 0.3509 if alcohol/metabolic, and 1.246 if viral
Sex indicates 0.5114 if male and 0 if female
Severity indicates a CTP score (5-15) × 0.1170
Step 2: baseline hazard at 1 year: S0(t) = 0.99986
Step 3: $[100*(1-S0(t)^{*}\exp^{(\text{ADRESS-HCC Score})}] =$ 1-year HCC risk (%)

Abbreviations: ADRESS, *a*ge, *d*iabetes, *r*ace, *e*tiology of cirrhosis, *s*ex, and *s*everity; CTP, Child-Turcotte-Pugh; HCC, hepatocellular carcinoma.

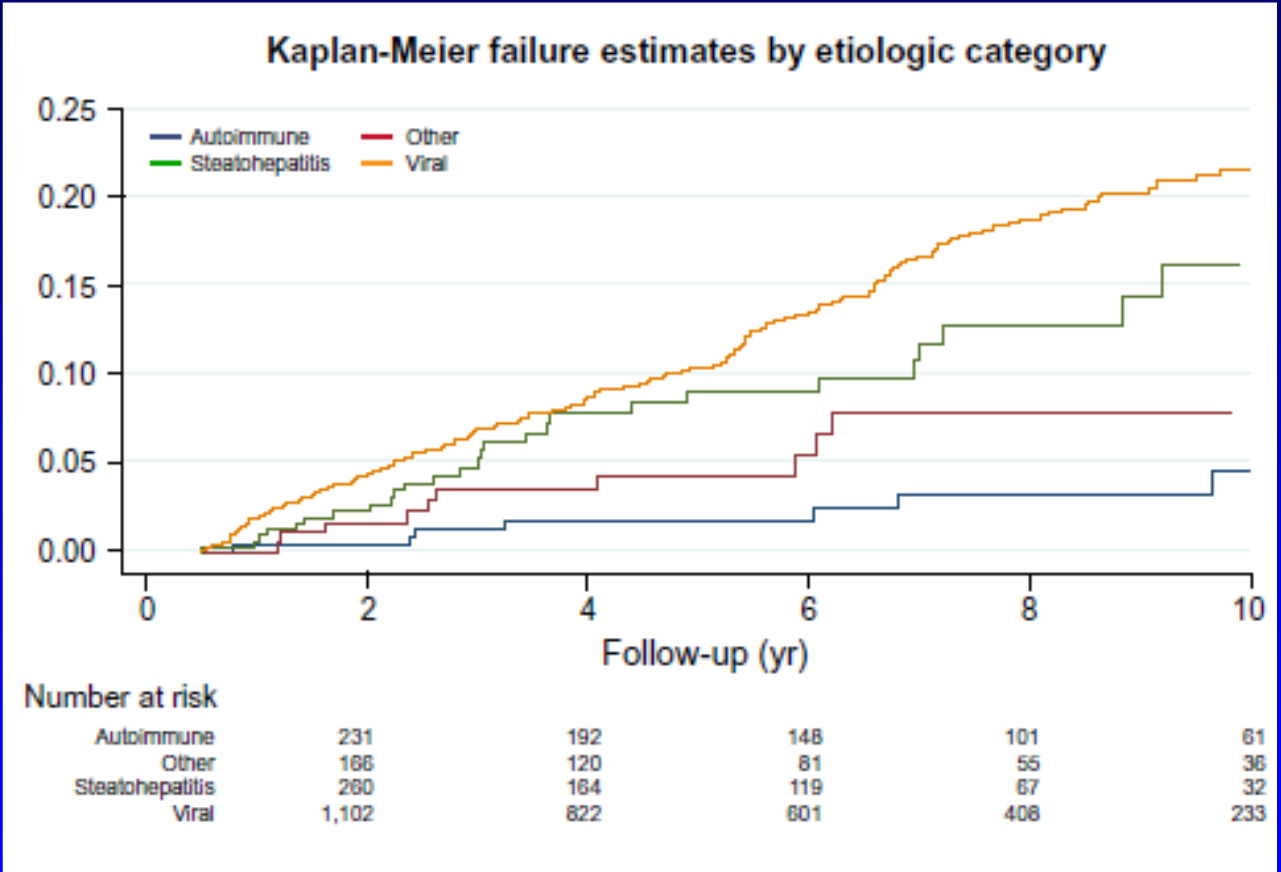
JA Flemming et al. Cancer 2014;120:3485-93.

Toronto HCC risk index for 10-year prediction in cirrhotics

THRI:
age, sex, etiology, platelets

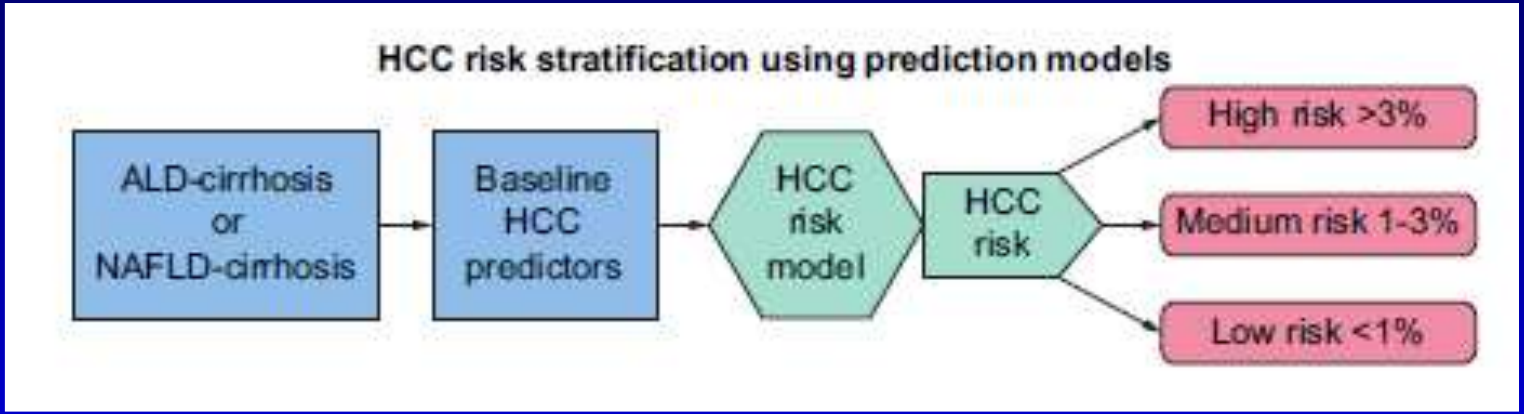
2,079 pts
(HCV: 42%, HBV: 19%, Alcohol: 11% NASH: 5% PBC: 5%)

AUROC: 0.76-0.77



SA Sharma et al. J Hepatol 2018;68:92-9.

Models of HCC risk in ALD/NAFLD cirrhotics



23,243 pts – ALD: 16,175, NAFLD: 7,068

White, non-Hispanic: 73%, Black, non-Hispanic: 10% Hispanic: 8%

HCC risk model: age, sex, BMI, diabetes, **PLT, albumin, AST/√ALT**

AUROCs: 0.72-0.74

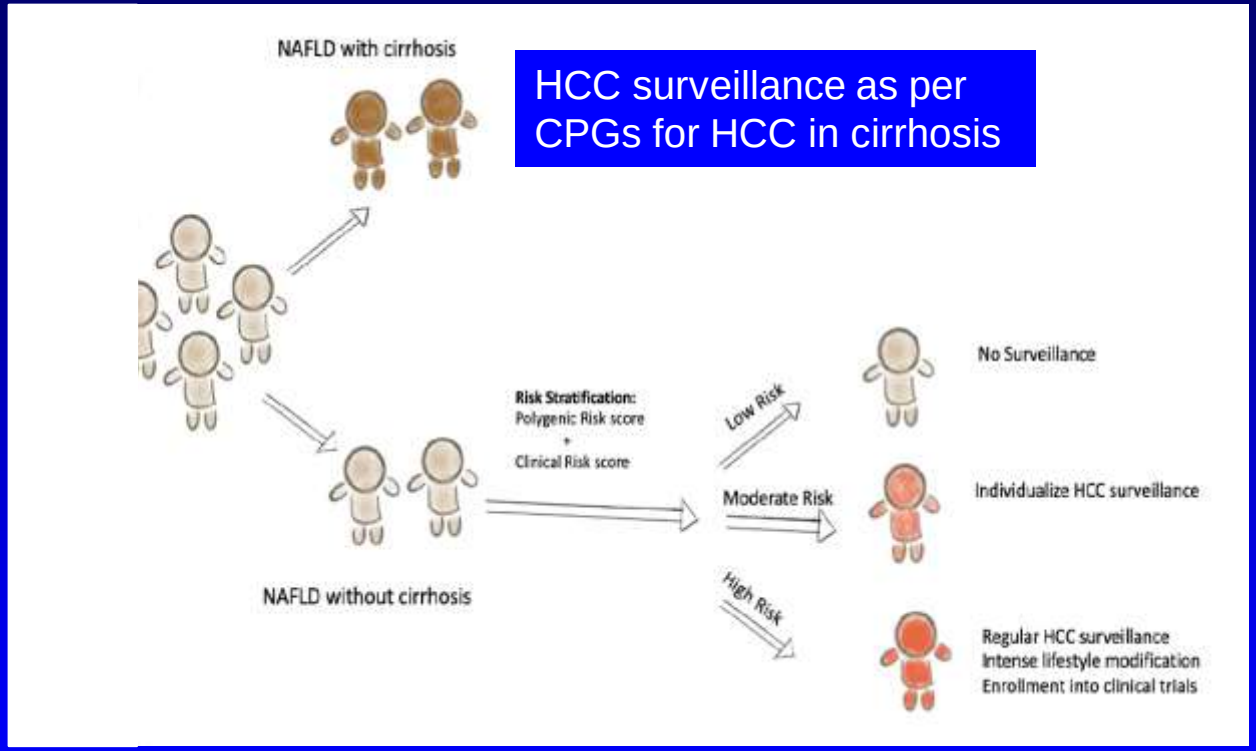
GN Ioannou et al. J Hepatol 2019;71:523-33.

Other HCC risk scores in NAFLD/ALD cirrhosis

Model	Country	Study Design	Output	Variables	Major Etiology	Predictive ability	Validation
Grimaudo S et al(96)	Italy	prospective longitudinal	aHR PNPLA3 G variant :2.68; P=.04 F3-F4 fibrosis (Inf P < .001)	PNPLA3 rs738409, F3-F4 fibrosis, Liver function, portal hypertension	NAFLD		No
APAC Score(97)	Germany	Observational cohort study		Age, sPDGFRβ, AFP, and Creatinine	NAFLD, viral, alcohol	AUROC 0.95 (95%, CI: 0.91-0.99) SN:84.62%, SP: 90.91% for HCC in NAFLD-cirrhosis	Internal

Shah PA et al. Hepatology 2022 Apr 28. doi: 10.1002/hep.32542.

HCC risk scores for patients with NAFLD without cirrhosis



- **Cost-effective HCC surveillance in non-cirrhotic NAFLD: individualization**
- **Non-cirrhotic NAFLD: No HCC surveillance if HCC risk 0.1-0.8 per 1,000 patient-years**

HCC risk score (age, sex, diabetes, smoking, cholesterol, ALT) for NAFLD without cirrhosis (No HBV/HCV/Alcohol): AUROC 0.83-0.92

n=467,206/91,357: derivation/validation cohort). **Sinn DH et al. Int J Epidemiol 2020;49:1562-71.**

Risk assessment of HCC development based on noninvasive surrogates

- **Non-invasive biomarkers of liver fibrosis severity**
- **HCC risk scores**
- **Emerging approaches**
  - ***Recent non-invasive biomarkers of HCC***
  - ***Prognostic models of HCC***

Recent non-invasive biomarkers of early HCC diagnosis

Biomarker	Phase of development	Early detection performance	AUC ROC for early detection
AFP (20–25)	5	Sensitivity: 39%–64% Specificity: 76%-97%	0.75–0.82
Lens culinaris agglutinin-reactive AFP (AFP-L3; refs. 20, 33)	2/3	Sensitivity: 49%–62% Specificity: 90%	0.66–0.76
DCP (20, 33)	2/3	Sensitivity: 34%–40% Specificity: 81%–98%	0.72
Osteopontin (38, 40, 41)	2	Sensitivity: 49% Specificity: 72%	0.73
MDK (44)	2/3	Sensitivity: 87% Specificity: 90%	0.923
DKK1 (45, 46)	2	Sensitivity: 41%–74% Specificity: 87%	0.61–0.88
GPC-3 (50–52)	2	Sensitivity: 55% Specificity: >95%	0.793
AFU (53)	2	Sensitivity: 56% Specificity: 69%	0.506
GP-73 (58, 59)	2	Sensitivity: 62%–79% Specificity: 62%–88%	Not available
SCCA (60–63)	2	Data for early-stage HCC not available	Data for early-stage HCC not available

Parikh ND et al. Cancer Epidemiol Biomarkers Prev 2020; 29:2495-503

Non-invasive biomarkers of HCC

- Germline genetic variants in
  (GWAS – SNPs)
- Germlin
  abolic related HCC
  2, MBOAT7 genes)
- iomarkers (cytokines, cfDNA species etc)

Might be useful for individual HCC-risk based screening in the future

Not widely validated

Not for clinical practice yet

Prognostic models of early HCC diagnosis

Table 3. Algorithms that have been evaluated for the detection of HCC.

Algorithms	Components	Phase of development	Early detection performance	AUC ROC for early detection
GALAD score (113)	Gender, age, AFP, AFP-L3, and DCP	2	Sensitivity: 68% Specificity: 95%	0.85–0.95
Doylestown + fucosylated kininogen (92)	Fucosylated kininogen, log AFP, age, gender, alkaline phosphatase, and ALT	2	7	0.97
HES algorithm (28)	Age, AFP, rate of AFP change, ALT, and platelet count	2/3	Data for early-stage HCC not available	Data for early-stage HCC not available
Methylated DNA panel (110)	4 methylated DNA markers, AFP, and AFP-L3	2	Sensitivity: 71% Specificity: 90%	0.91

Parikh ND et al. Cancer Epidemiol Biomarkers Prev 2020; 29:2495-503

GAAD score (age, gender, aFP, PIVKA-II) vs GALAD score: better detection of early stage HCC.

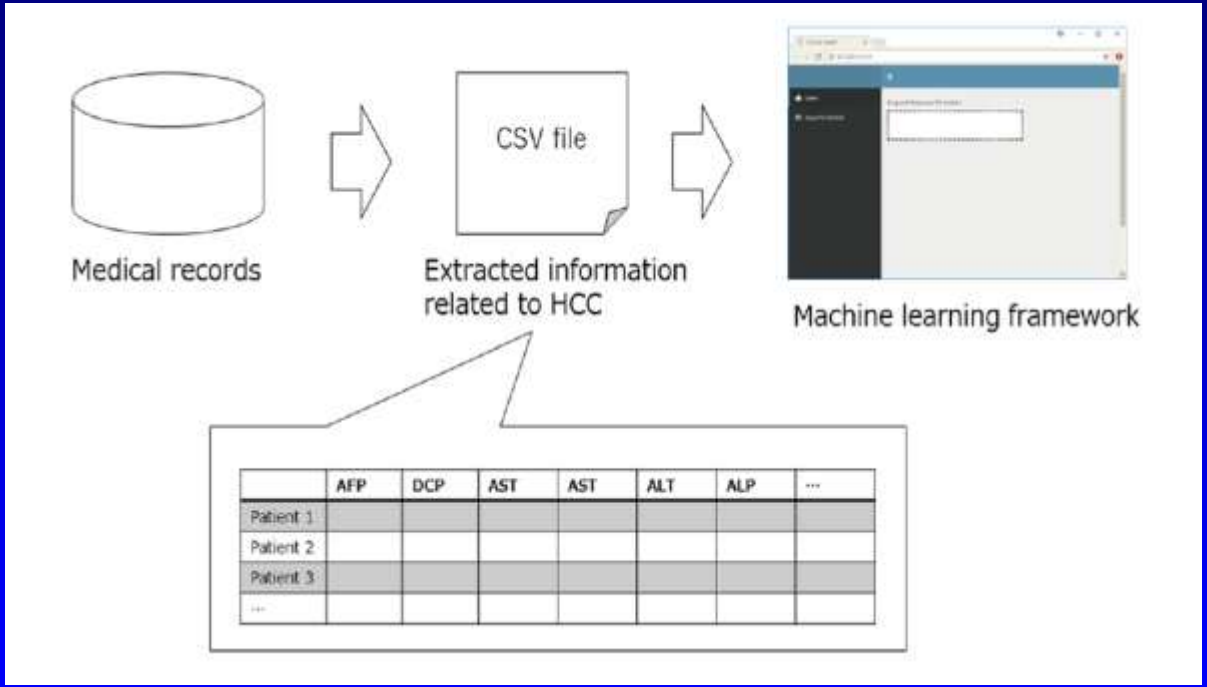
HLA Chan et al. J Hepatol 2022;77:S937.

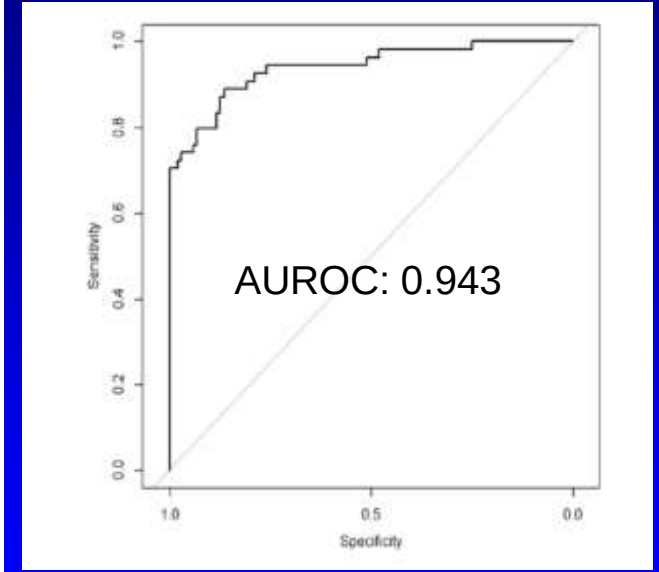
Prognostic models for HCC in NAFLD without cirrhosis

Model	Study Design	Variables	Population	Country	Predictive ability (AUROC, HR)	Validation
Gellert-Kristenson et al(105)	Prospective	PRS: PNPLA3+TM6SF2+HSD17B13	General population	UK Denmark	HR 29 (95% CI, 17, 51), p<0.001	No
Pelusi et al.(101)	Retrospective Cohort	PRS: PNPLA3+TM6SF2+MBOAT7+Variants Clinical: Age, gender, obesity, T2DM, severe fibrosis	NAFLD with NCL	Italy UK Non-Finnish Europeans	0.9 ± 0.04 (93% SN, 86% SP)	Yes
Donati et al(100)	Retrospective Cohort	PRS: PNPLA3, TM6SF2and MBOAT7 Clinical: Age, gender, obesity, T2DM, severe fibrosis	NAFLD with NCL	Italy	0.96 ± 0.04 (96% SN, 89% SP)	No

Shah PA et al. Hepatology 2022 Apr 28. doi: 10.1002/hep.32542.

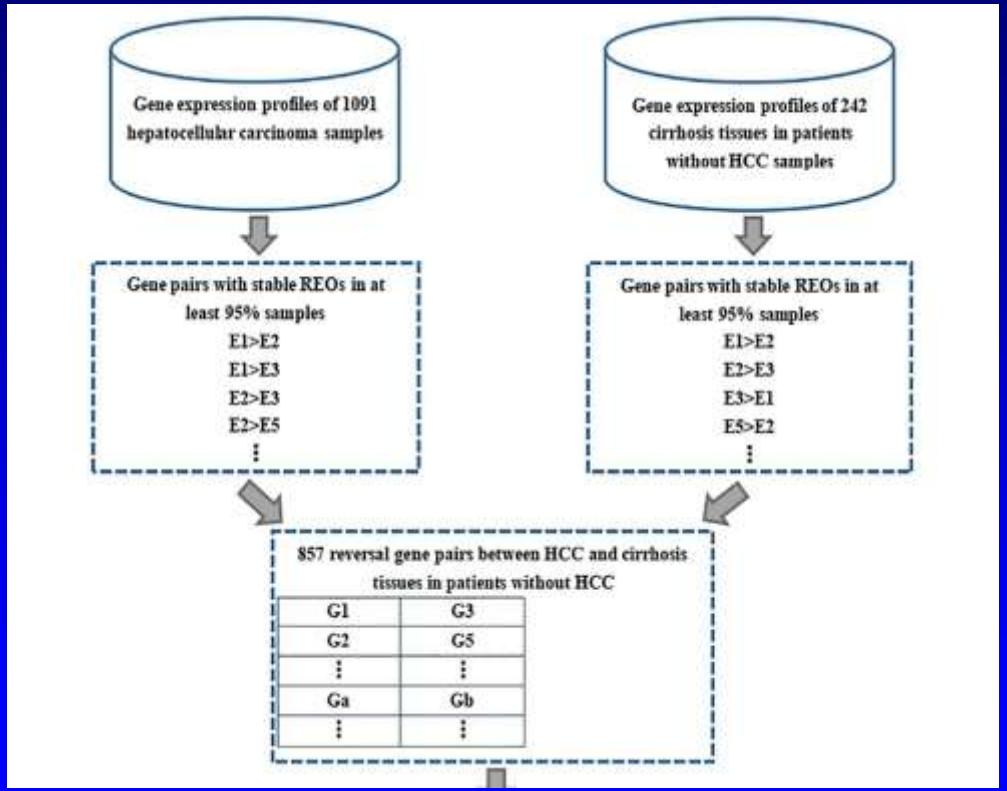
New approaches for HCC diagnosis: Prognostic models of biomarkers using AI-Machine learning

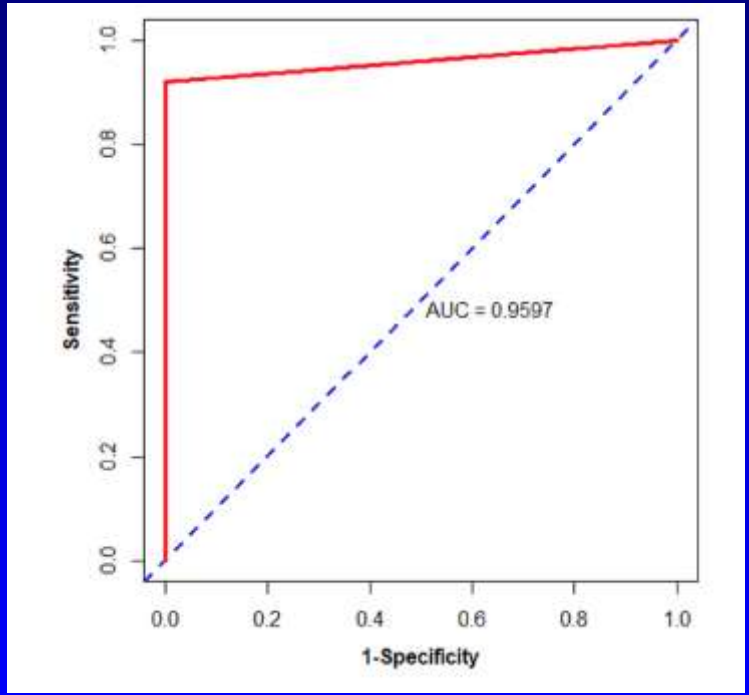




Sato M. et al. Sci Rep 2019; 9:7704

New approaches for HCC diagnosis: Prognostic models of gene pairs using AI-Machine learning



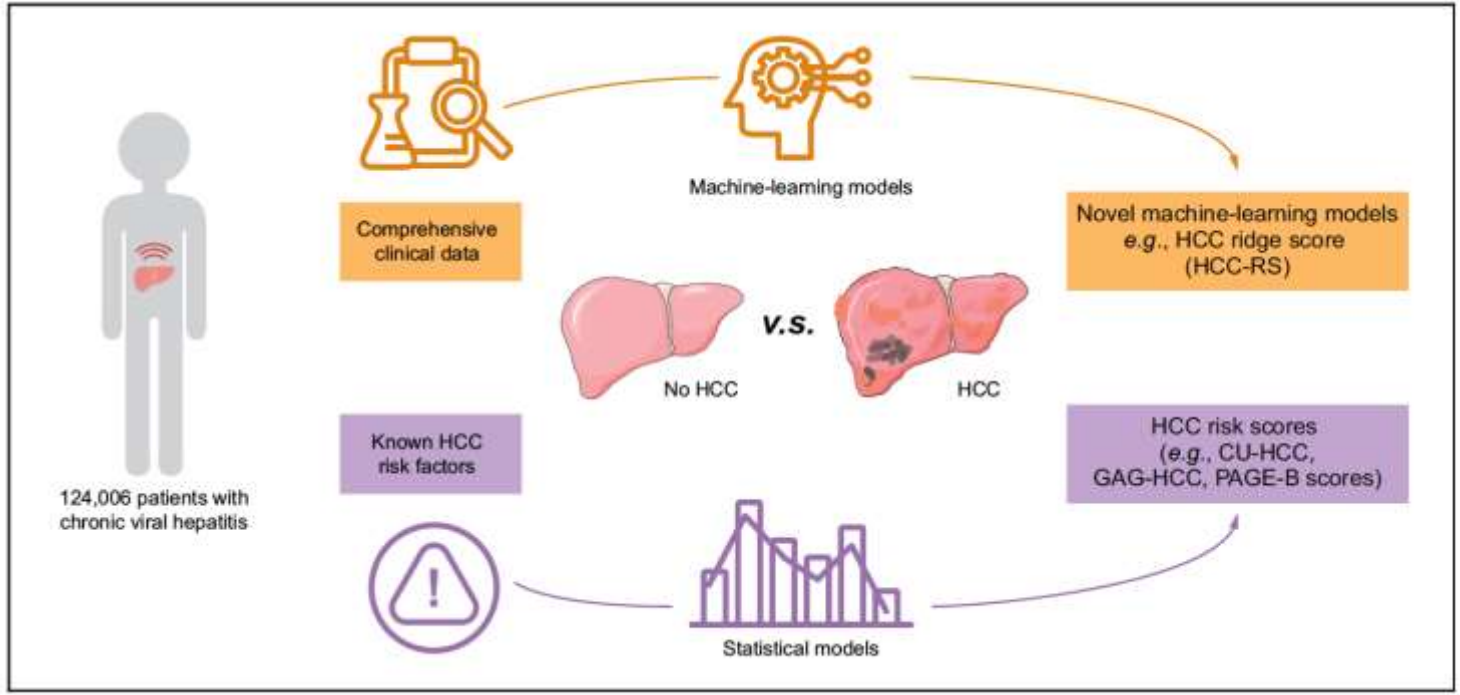


Zhang et al. Front Bioeng Biotechnol 2021;8:254.

Machine Learning Algorithms Outperform Conventional Regression Models in Predicting Development of Hepatocellular Carcinoma

Amit G. Singal, MD MS[1,2,3], Ashin Mukherjee, MS[4], B. Joseph Elmu
Higgins, MD PhD[5], Anna S. Lok[5], Ji Zhu, PhD[4], Jorge A Marrero, MI
Waljee, MD MS[5,6]

Novel machine learning models outperform risk scores in predicting hepatocellular carcinoma in patients with chronic viral hepatitis



Risk assessment of HCC development based on noninvasive surrogates - Conclusions

- HCC risk: mainly depends on the severity and cause of liver disease
- Epidemiological factors are important (age>gender)
- CHB: mostly studied – HCC risk scores can be useful depending on the CHB setting - PAGE-B: one of the simplest and the most well validated HCC risk score; the only score included in CPGs
- Efforts including risk scores for specific risk assessment in other settings (eg HCV after SVR, ALD/NAFLD); not in clinical practice yet

Risk assessment of HCC development based on noninvasive surrogates - Conclusions

- Many new HCC risk scores and biomarkers based on clinical/laboratory parameters, genes and/or new biomarkers: under evaluation

- Artificial intelligence - machine learning: new potential for individualized more accurate HCC risk assessment in the future

Thank you for your attention!