MÁSTER EN HEPATOLOGÍA

UAM Universidad Autónoma de Madrid

Universidad de Alcalá

Asignatura: Problemas clínicos y controversias en hepatología

“Cribado del HCC en cirrosis : el camino hacia la personalización”

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Cribado del HCC en cirrosis : el camino hacia la personalización

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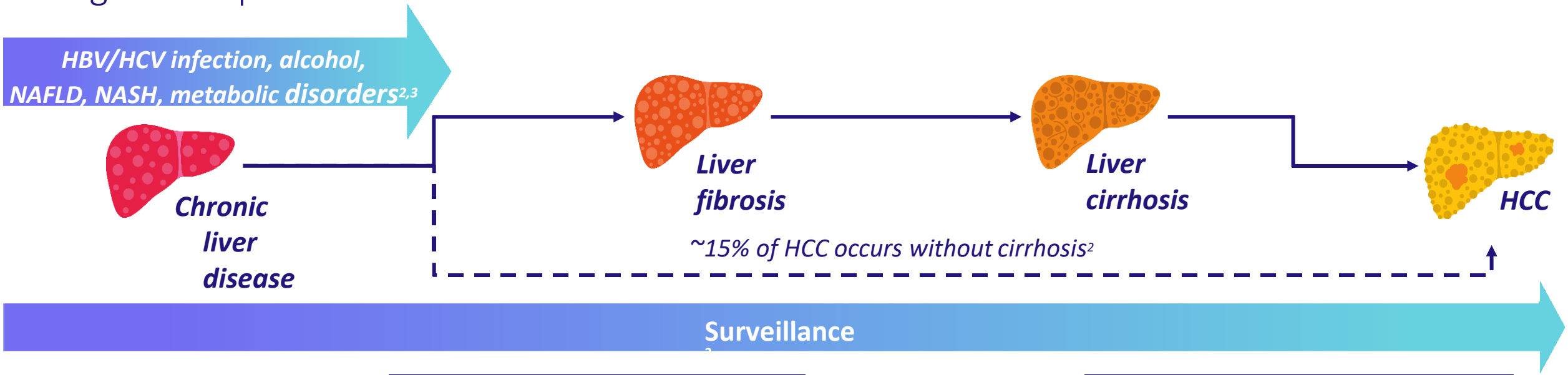
INVESTIGACIÓN PUERTA DE HIERRO

Liver cancer is the third-leading cause of cancer mortality:[1] surveillance and early diagnosis improve survival rates

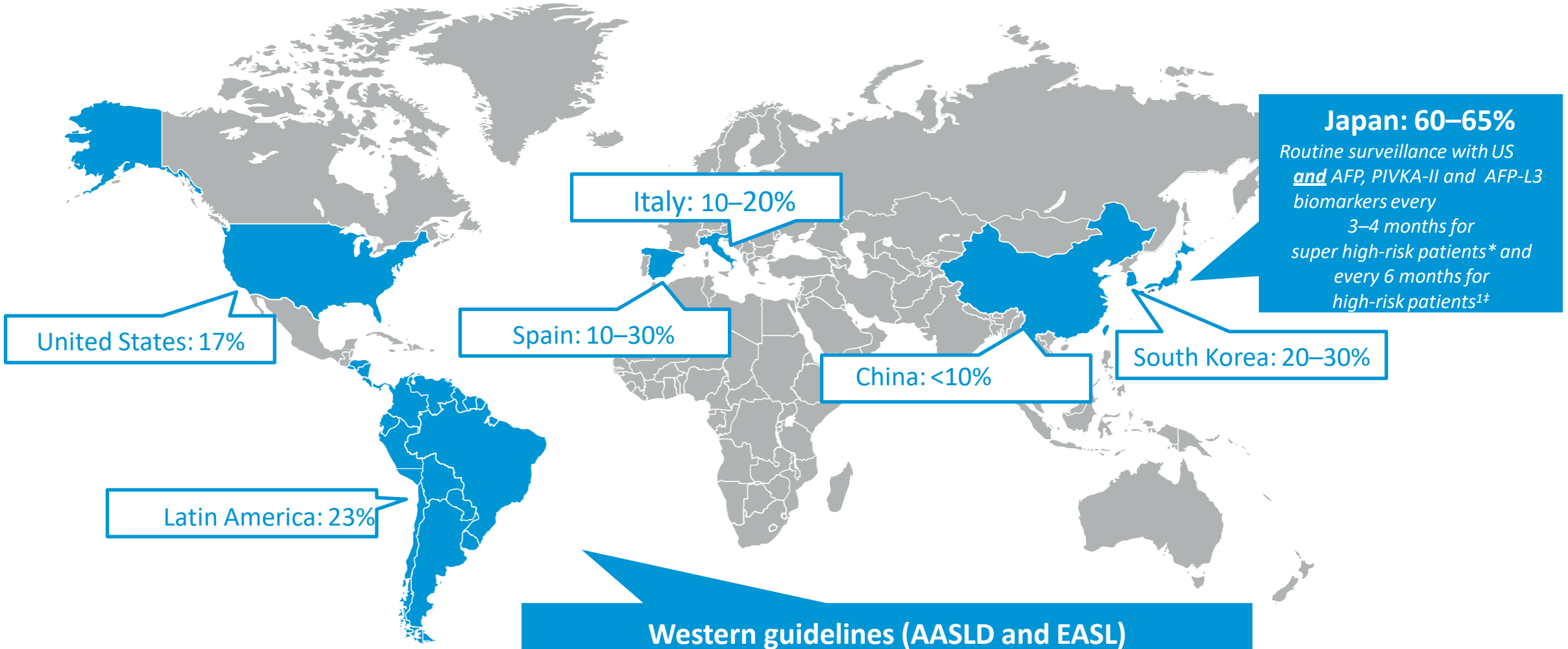


	Early diagnosis of HCC		Late diagnosis of HCC
HCC diagnosis pathway	**Asymptomatic,[4] detected through screening[3]**	Symptoms occur, most commonly pain, fatigue, weight loss, jaundice and ascites[6]	**Symptomatic,[3,4] detected through diagnostic algorithm**
Treatment	Diagnosis at early stage allows resection and gives choice of therapies[4,5]		Only 20–30% of patients fulfil resection criteria due to late diagnosis[7]
5-year survival rate	50–70%[5]		10–15%[5]

HBV, hepatitis B virus; HCV, hepatitis C virus
NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis

1. Sung et al. Ca Cancer J Clin 2021; 2. Marquardt et al. Nat Rev Cancer 2015
3. Llovet et al. Nat Rev Dis Primer 2016; 4. Singal et al. PLoS Med 2014
5. Allaire et al. JHEP Reports 2020; 6. Sun and Sarna et al. Clin J Oncol Nurs 2008
7. Zhou et al. Liver Cancer 2020

The rate of early-stage (BCLC stage 0/A) HCC at initial diagnosis varies across the world[1]



*Cirrhosis caused by HBV or HCV; ‡HBV, HCV and non-viral cirrhosis BCLC, Barcelona Clinic Liver Cancer

1. Kudo et al. Liver Cancer 2018
2. Purcell et al. Ultrasonography 2019

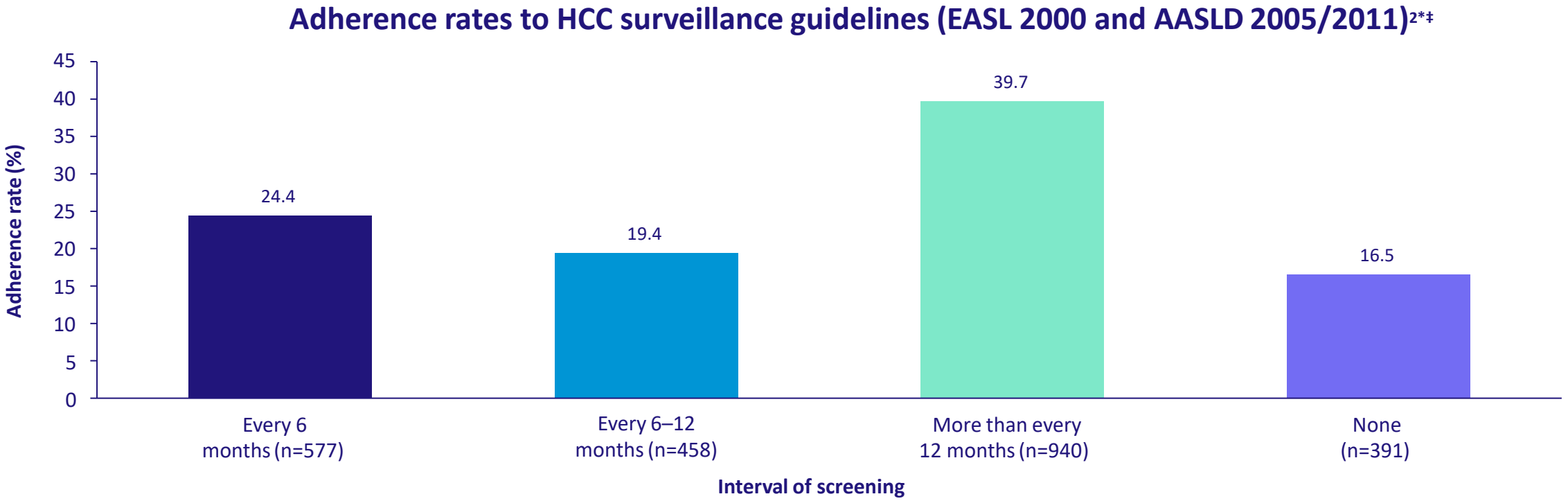
Current recommendations for HCC surveillance

		Western		Eastern		
		AASLD	**EASL**	**JSH**	**APASL**	**KLCA**
Super-high-risk patients	**Definition**	–	–	Cirrhosis with HBV or HCV	–	–
	Modality			Liver US + AFP/AFP-L3, PIVKA-II CT/EOB-MRI		
	Interval			3–4 mo, CT/MRI 6–12 mo		
High-risk patients	**Definition**	Cirrhosis*	Cirrhosis,* HBV,‡ F3	Cirrhosis of any cause, HBV, HCV	Cirrhosis with HBV or HCV	Cirrhosis of any cause, HBV, HCV
	Modality	Liver US ± AFP	Liver US	Liver US + AFP/ AFP-L3, PIVKA-II CT/EOB-MRI	Liver US AFP§	Liver US AFP¶
	Interval	6 mo	6 mo	6 mo No CT/EOB-MRI	6 mo	6 mo

AASLD, American Association for the Study of Liver Diseases; AFP, alpha fetoprotein; APASL, Asian Pacific Association for the Study of the Liver EASL, European Association for the Study of the Liver; JSH, Japanese Society of Hepatology; KLCA, Korean Liver Cancer Association
F3, fibrosis stage 3 according to the METAVIR system; SVR, sustained virologic response
*Child-Pugh A or B, and Child-Pugh C awaiting liver transplantation; ‡According to PAGE-B classes
§Accepted diagnostic cut-off value >200ng/mL even though the measurement is not recommended
¶For nodules <1cm

1. Purcell et al. Ultrasonography 2019
2. Frenette et al. Mayo Clin Proc Innov Qual Outcomes 2019

Eastern countries have systematic surveillance programmes while most Western countries rely on individual adherence[1,2]



24% of patients underwent HCC surveillance every 6 months

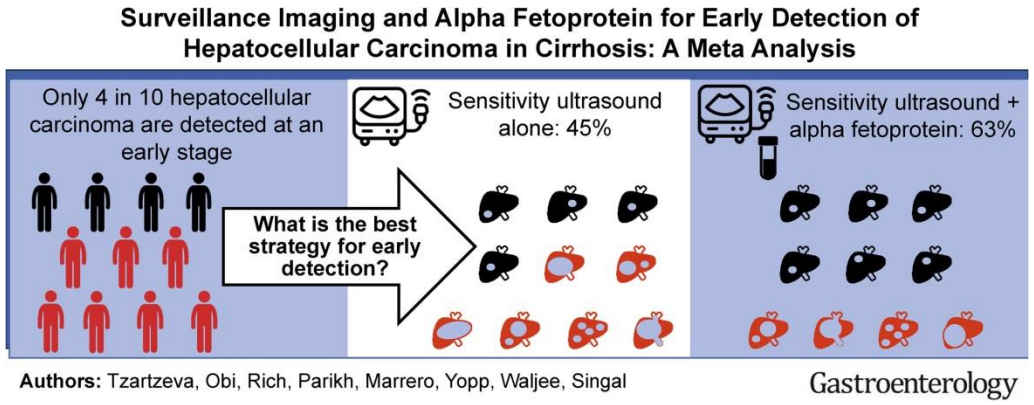
44% of patients underwent HCC surveillance at least every 12 months[2]

*Patients with HCV cirrhosis monitored for at least a year at Stanford University Medical Center between January 2001 and August 2015

‡Surveillance recommendation changed from every 6–12 months in 2005 to every 6 months in 2011

1. Purcell et al. Ultrasonography 2019
2. Tran et al. BMJ Open Gastroenterol 2018

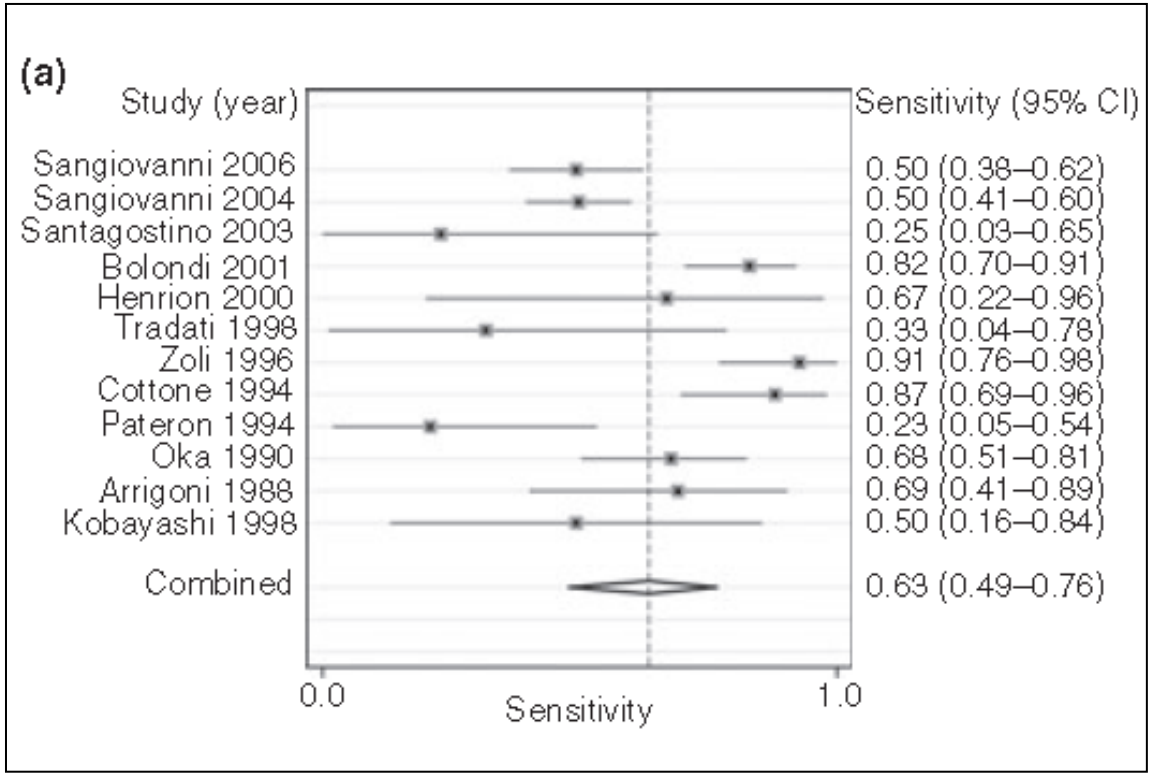
Surveillance performance



Sensitivity 63%, Specificity 84%

1/3 diagnosis under surveillance: non early HCC

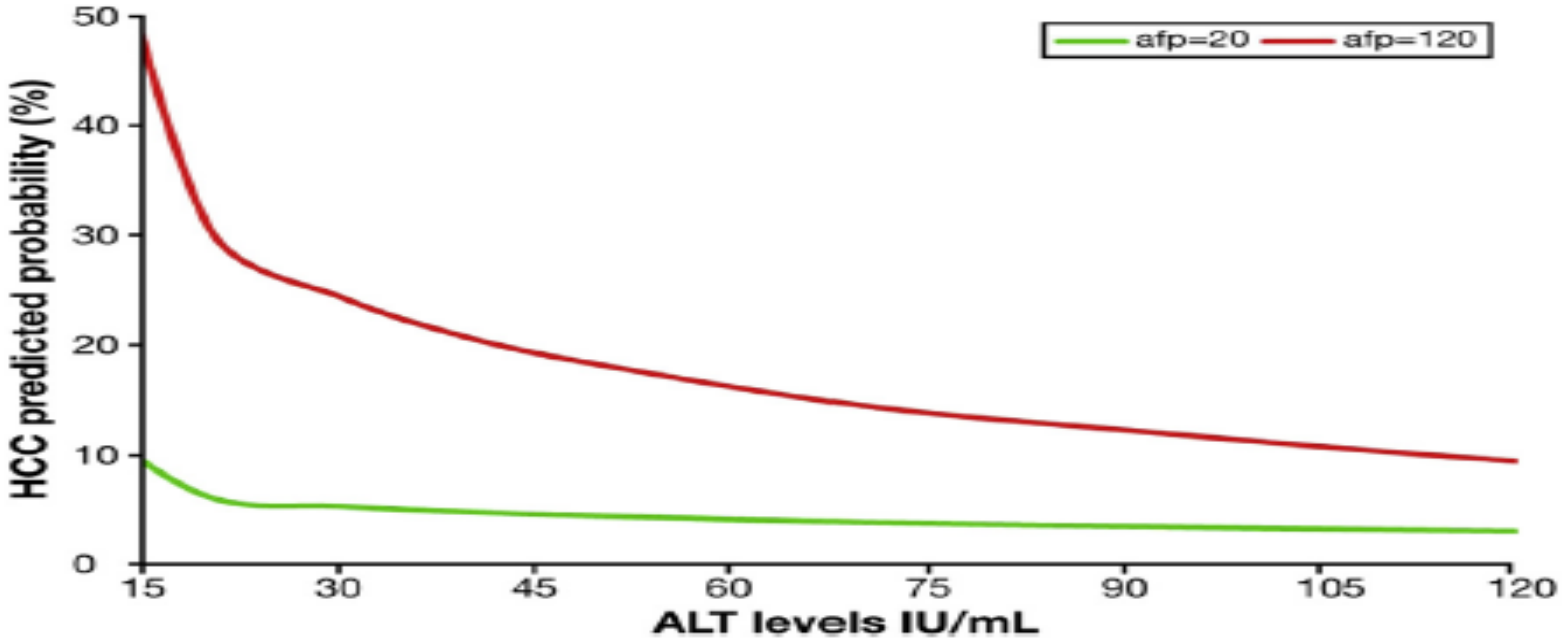
US in early HCC



Sensitivity 69%, Specificity 74%

Singal APT 2009
Tzartzeva et al Gastroenterology 2018
Wolf E et al, Hepatology 2020

Performance of AFP

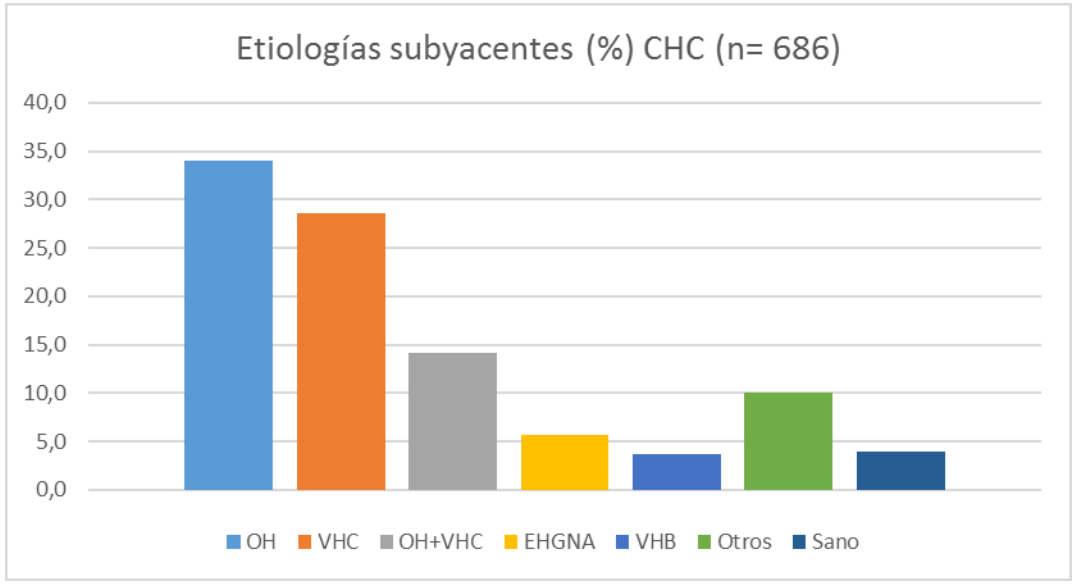


El Serag Gastro 2004

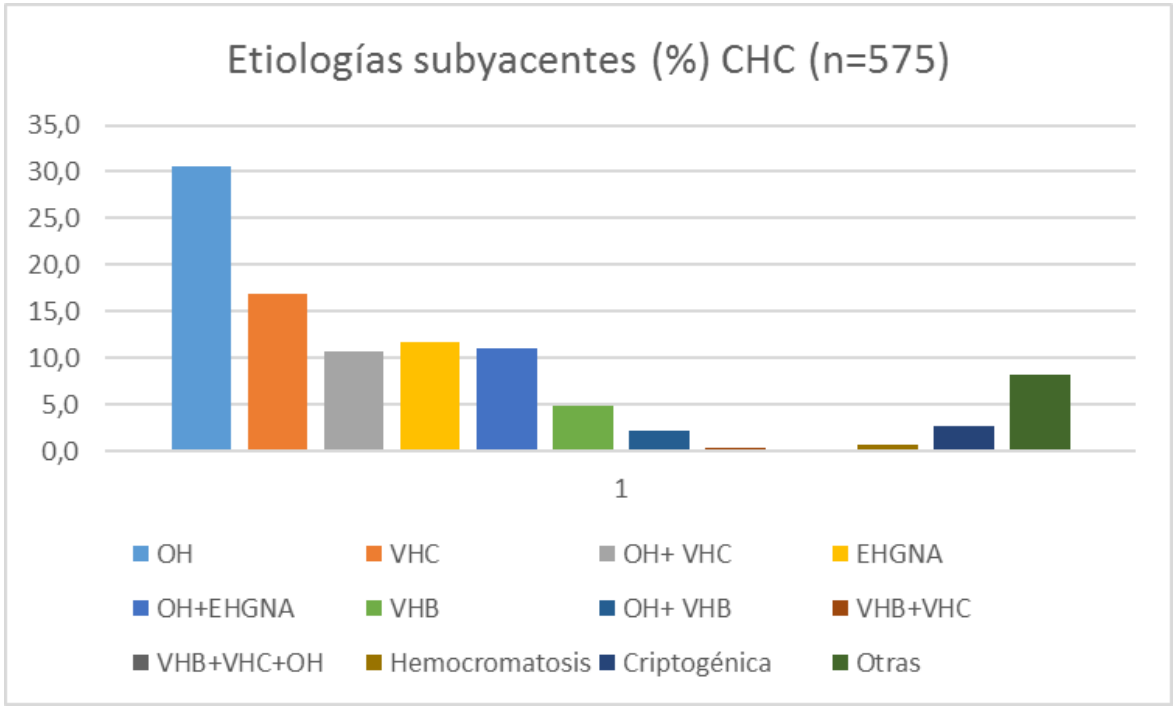
AEEH

registroHCC

Segundo registro HCC AEEH:
Octubre 2014 - Enero 2015



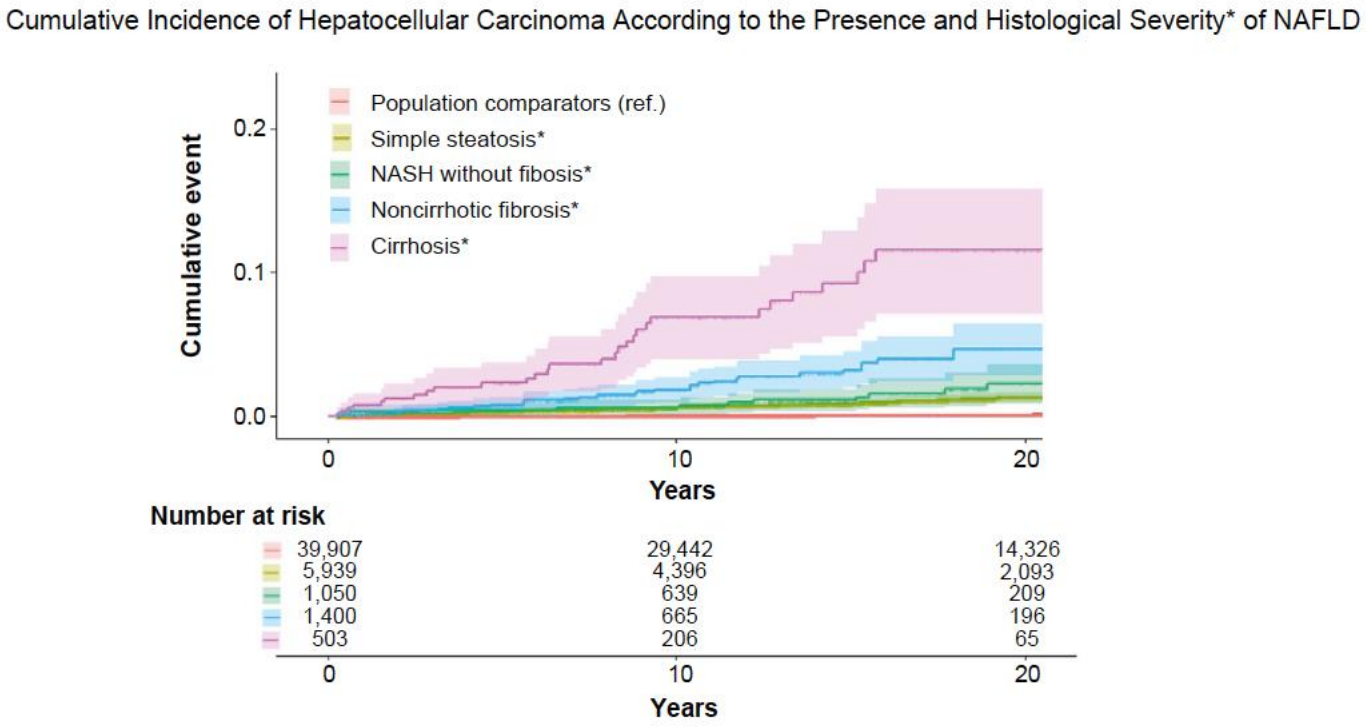
Tercer Registro HCC AEEH:
Recogida prospectiva de nuevos casos CHC
Octubre 2022 - Enero 2023
(n=645)
Datos preliminares



Análisis en curso. Datos del 89.1% de los pacientes, los resultados finales pueden presentar variaciones

Rodriguez de Lope C et al Med Clin C 2017
Datos preliminares no publicados del 3er registro HCC. Cortesía Dra Varela y Dra Sala

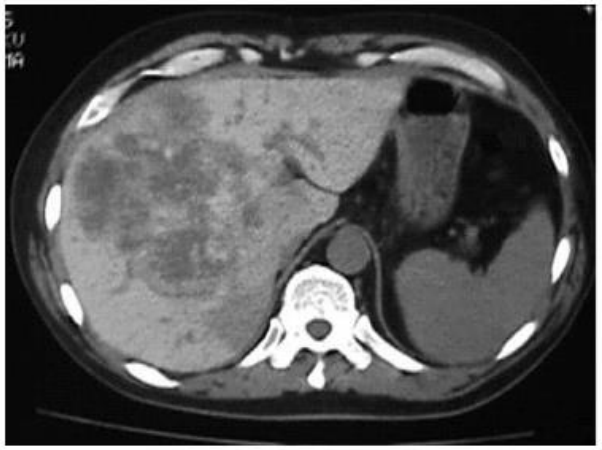
Riesgo de HCC y NAFLD

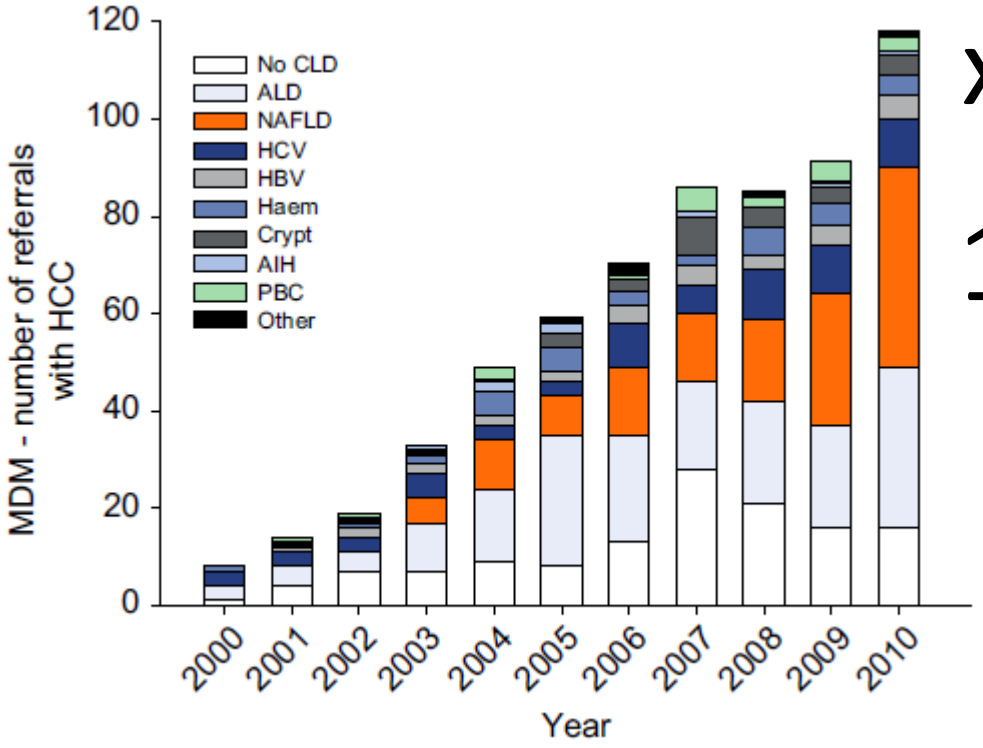


Simon TG et al Hepatology 21

Hepatocellular carcinoma (HCC)

NASH is becoming the first cause of HCC in the UK/USA





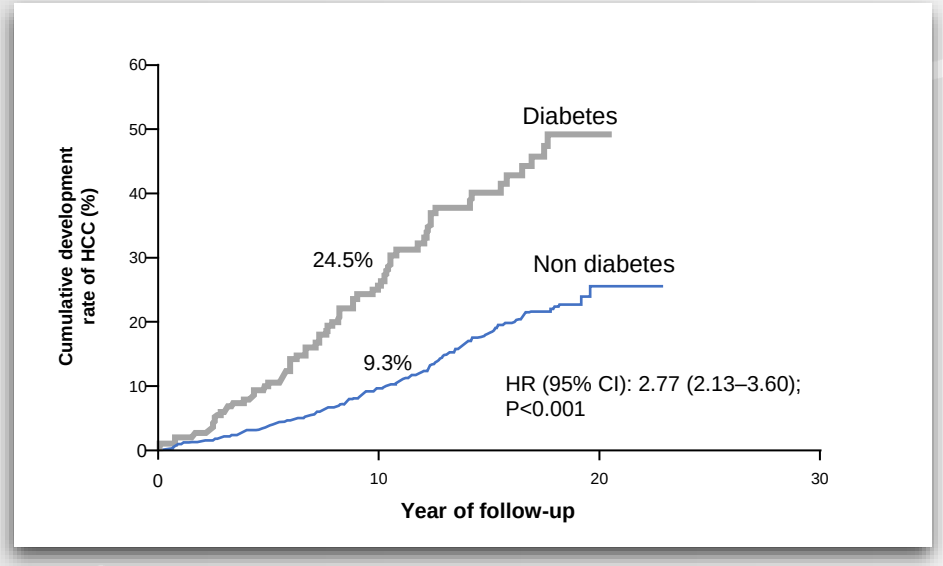
x10!

1/3!

Dyson, J Hepatol 2014; Wong, Hepatology 2014

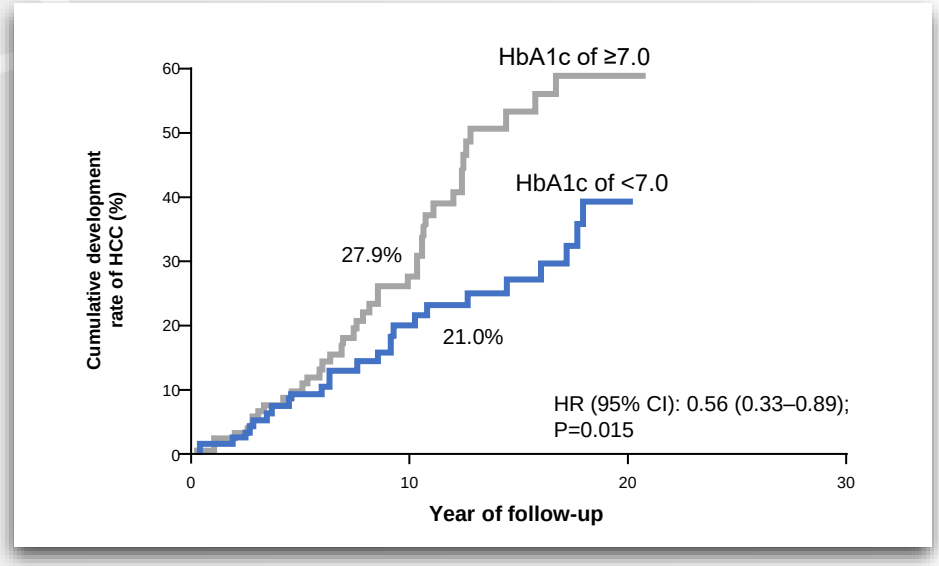
La DMT2 causa mayor riesgo de desarrollo de CHC (≈1,7 veces)

Cumulative development rate of HCC based on the difference of diabetic state in T2DM patients



Glucose state	0y	5y	10y	15y	20y
Diabetes (n)	267	172	102	49	2
Non-diabetes (n)	4035	2593	1474	553	43

Cumulative development rate of HCC based on the difference mean HbA1c level in T2DM patients

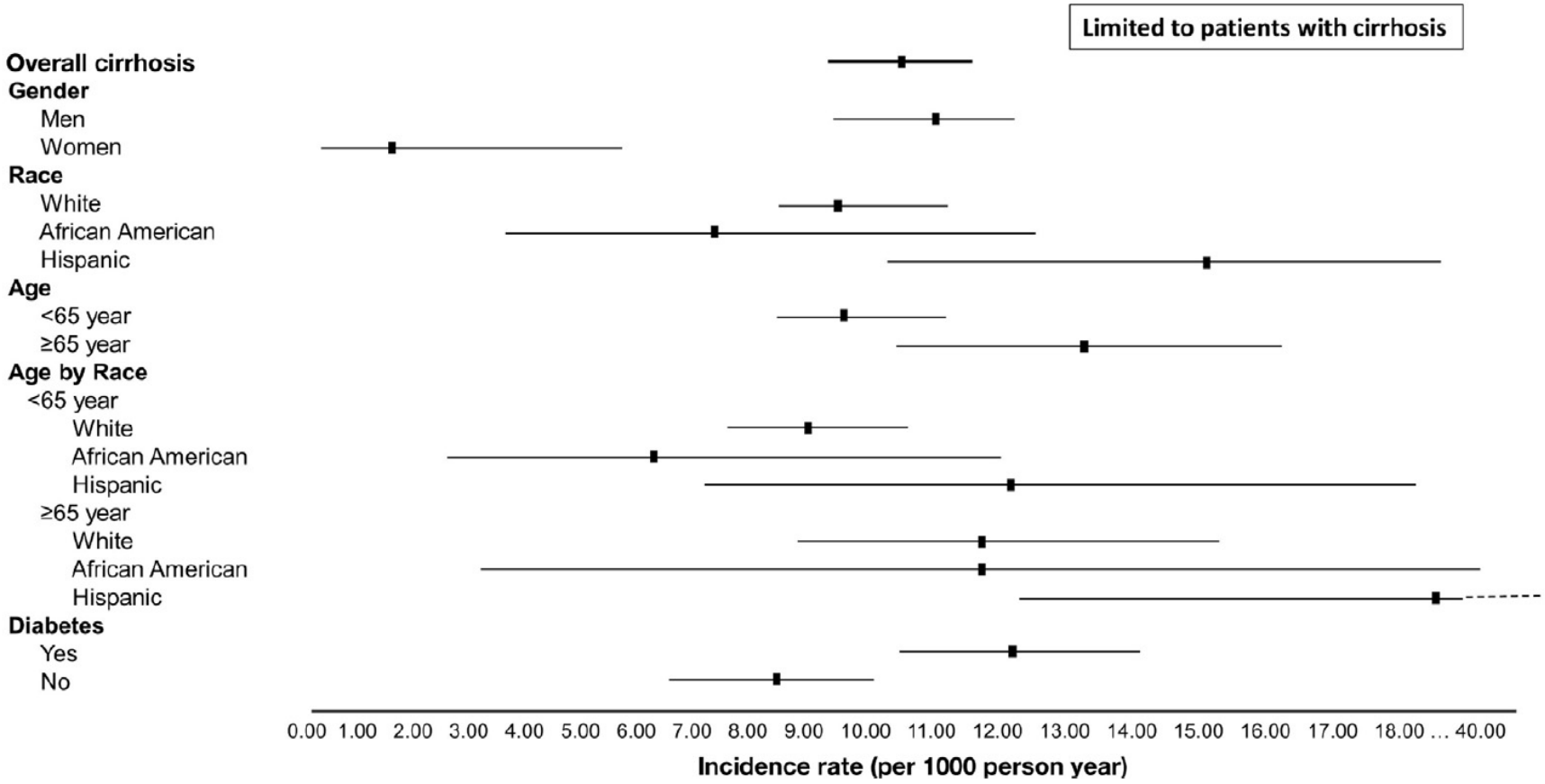


HbA1c	0y	5y	10y	15y	20y
≥7.0 (n)	140	90	48	18	1
<7.0 (n)	127	82	54	31	1

HbA1c: glycated haemoglobin;
HCC: hepatocellular carcinoma; T2DM: type 2 diabetes mellitus

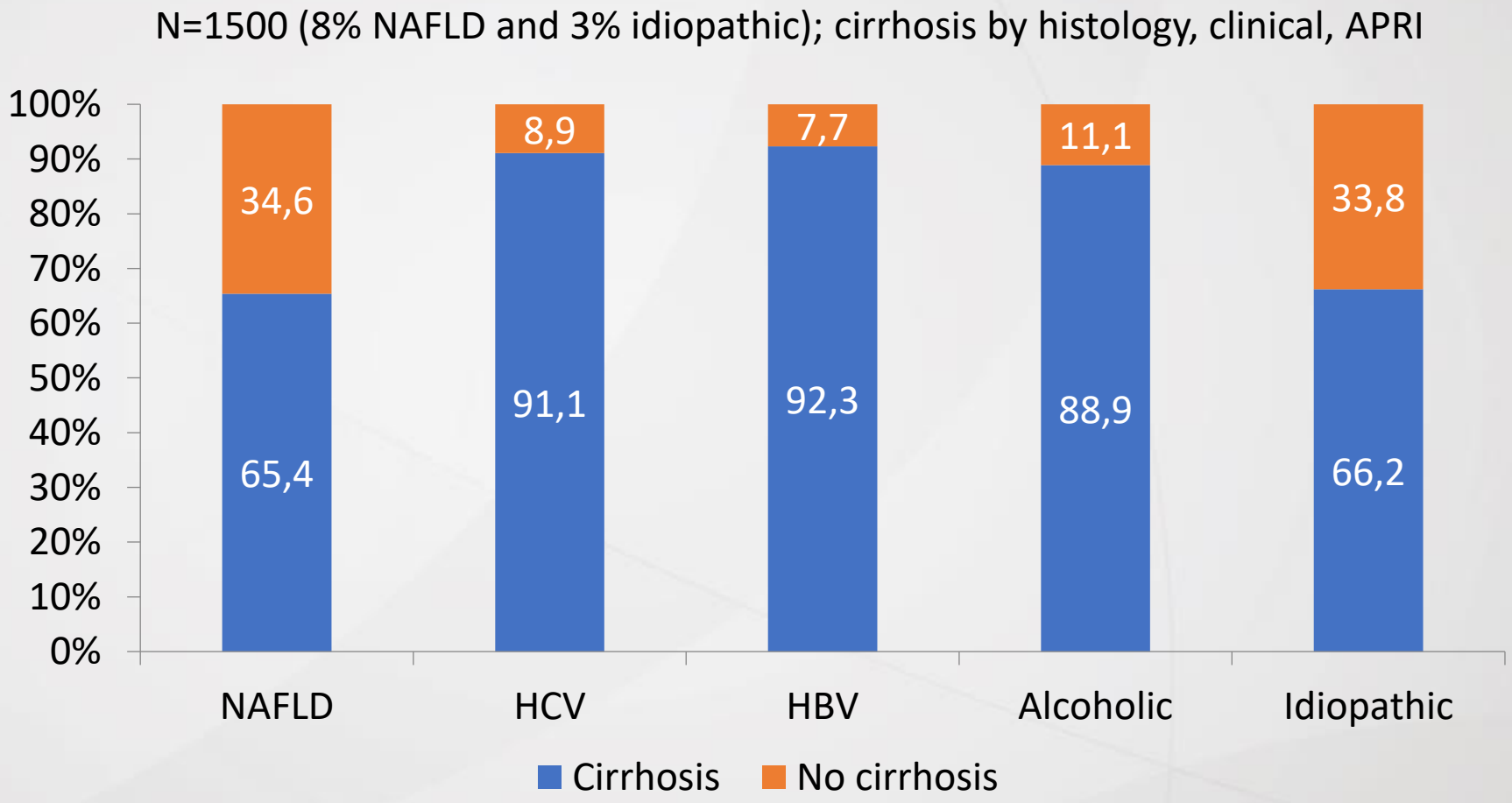
Arase Y, et al. Hepatology 2013;57:964–73

NAFLD y Riesgo de HCC



Simon TG et al Hepatology 21

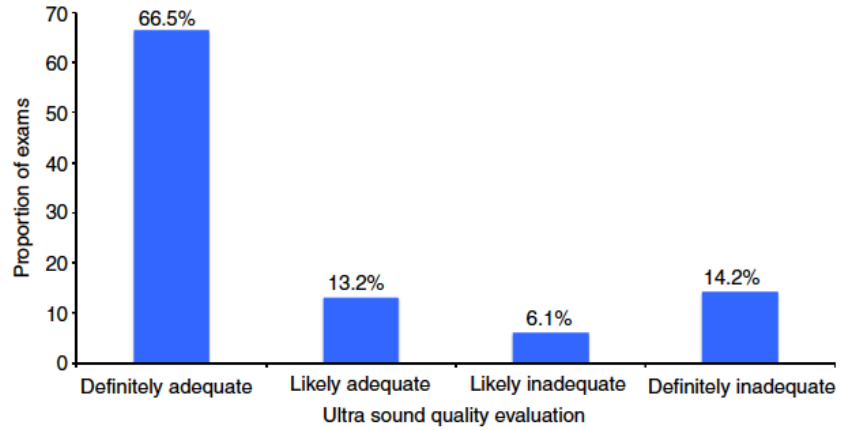
Non-cirrhotic HCC in the VA cohort



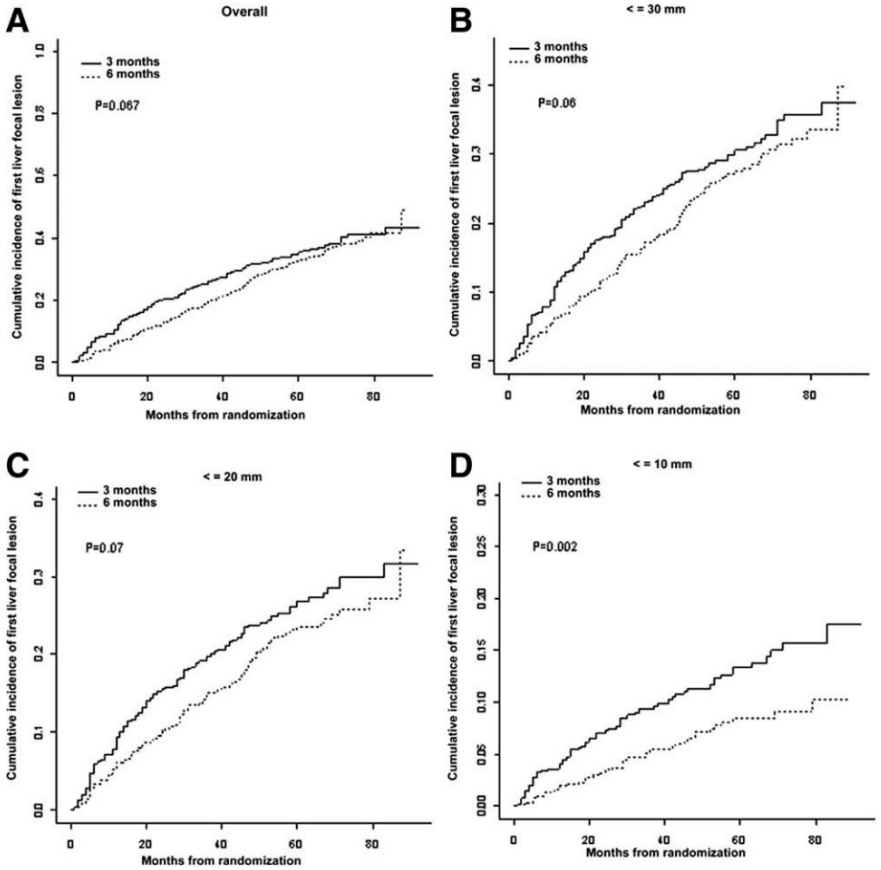
Mittal et al. Clin Gastroenterol Hepatol 2016;14:124

Performance of US

Characteristic	Univariate analysis		Multivariable analysis	
	OR	95% CI	OR	95% CI
Male gender	1.42	1.01–2.01	1.68	1.14–2.48
Child Pugh B or C cirrhosis	2.17	1.56–3.00	1.93	1.32–2.81
BMI category				
Normal (BMI <25)	Ref	Ref	Ref	Ref
Overweight (BMI 25–29.99)	2.12	1.28–3.54	2.29	1.35–3.88
Obesity class II (BMI 30–34.99)	2.88	1.70–4.89	2.95	1.67–5.20
Obesity class II (BMI 35–39.99)	5.35	2.96–9.66	6.37	3.35–12.12
Morbid obesity (BMI ≥40)	6.29	3.45–11.47	8.22	4.30–15.73
Aetiology of liver disease				
Hepatitis C	Ref	Ref	Ref	Ref
Hepatitis B	1.09	0.49–2.42	1.87	0.79–4.39
Alcohol-related	2.73	1.80–4.16	2.11	1.33–3.37
Non-alcoholic steatohepatitis	3.16	1.97–5.07	2.87	1.71–4.80
Other	0.66	0.23–1.93	0.67	0.22–2.04
ALT >40 U/L	0.70	0.50–0.97	0.93	0.64–1.34
In-patient status	1.55	1.08–2.23	1.55	1.01–2.37



Room for improvement: shorter intervals



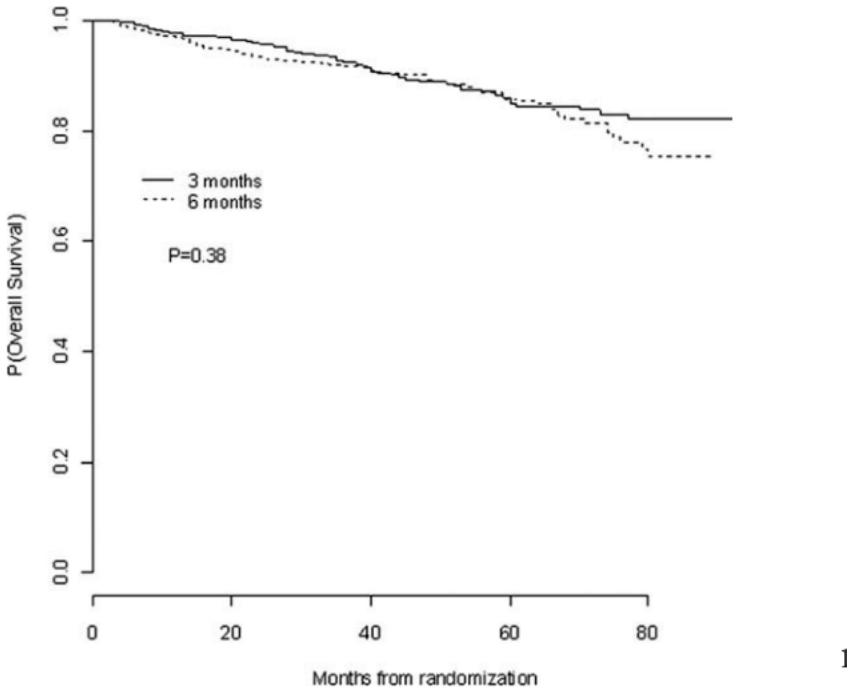


Fig. 4. Overall survival according to randomization ($P = 0.38$).

Trinchet JC Hepatology 2011

Room for improvement : MRI

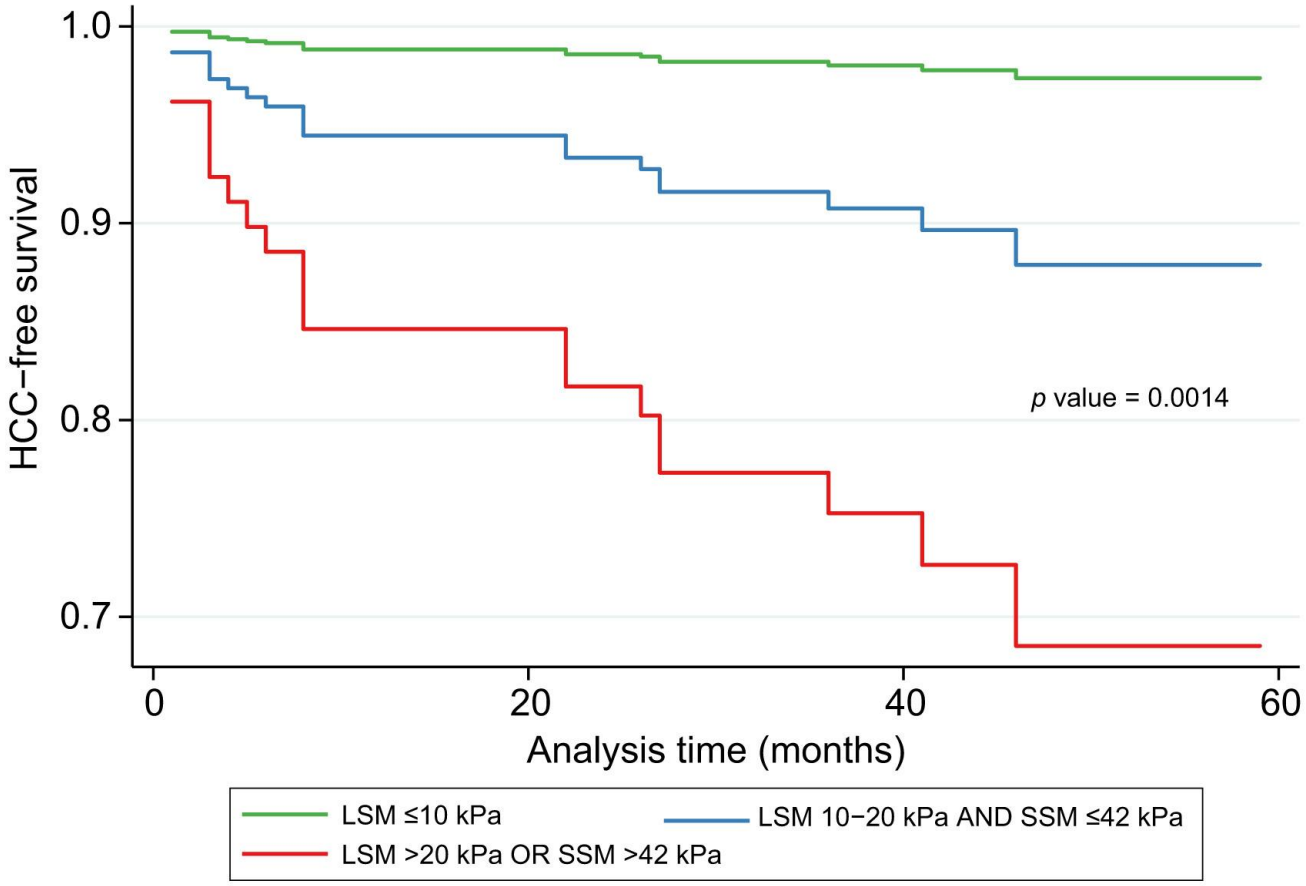
Table 2. Summary of Meta-Analyses on the Diagnostic Performance of AMRI for Hepatocellular Carcinoma Detection

Study	Year	Total Number of AMRI Studies	Number of Studies Performed in a Diagnostic Setting	Number of Studies Performed in a Surveillance Setting	Pooled Sensitivity (%)*	Pooled Specificity (%)*
Gupta et al. [13]	2021	15	7	8	86 (84–88)	94 (91–96)
Chan et al. [14]	2021	22	18	4	86.8 (83.9–89.4)	90.3 (87.3–92.7)
Kim et al. [5]	2021	10	3	7	86 (80–90)	96 (93–98)
Kim et al. [15]	2021	4	1	3	87 (80–94)	94 (90–98)

*Numbers in parentheses are 95% confidence intervals. AMRI = abbreviated MRI

Kim SY KJR 2022

Room for improvement : SSM Associated with Risk of HCC



- **SSM at SVR24 predicted HCC** development in univariate and adjusted multivariate analysis (hazard ratio: 1.025; 95% CI: 1.001–1.050); **the best cut-off was 42 kPa**.
- Patients with **LSM-SVR24 ≤10 kPa** were at the lowest risk of HCC.
- In patients with **LSM-SVR24 >10 kPa**, HCC incidence was not further influenced by LSM values (10–20 kPa vs. >20 kPa), but only by SSM-SVR24 values (≤42 vs. >42 kPa).

Dajti et al. JHEPReport 2021 3DOI: (10.1016/j.jhepr.2021.100289)

Room for improvement : risk stratification

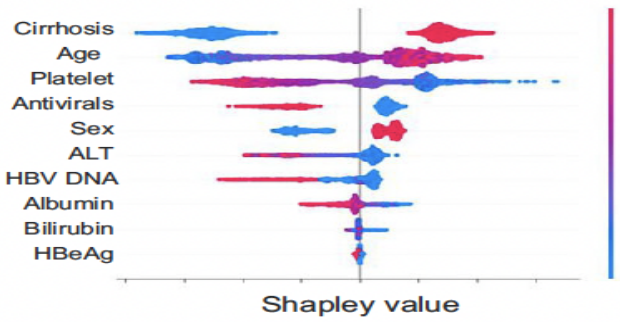
HCC risk score	Low/High-risk group cut-off	AUROC, c-statistic (95% CI)	Sensitivity, %	NPV, %
At baseline		5-year HCC prediction		
PAGE-B	10/18	0.80 (0.76, 0.83)	99.3%	99.8%
HCC-Rescue	65/85	0.81 (0.78, 0.84)	97.2%	99.5%
CAMD	8/14	0.79 (0.74, 0.83)	100%	100%
mPAGE-B	9/13	0.82 (0.78, 0.85)	97.8%	99.3%
AASL	6/20	0.81 (0.77, 0.84)	99.3%	99.7%
At baseline		10-year HCC prediction		
PAGE-B	10/18	0.78 (0.75, 0.81)	99.3%	99.8%
HCC-Rescue	65/85	0.81 (0.79, 0.84)	97.2%	99.5%
CAMD	8/14	0.80 (0.76, 0.83)	100%	100%
mPAGE-B	9/13	0.81 (0.78, 0.84)	97.8%	99.3%
AASL	6/20	0.80 (0.77, 0.83)	99.3%	99.7%

Papatheodoridis G et al J Hep Rep 2021

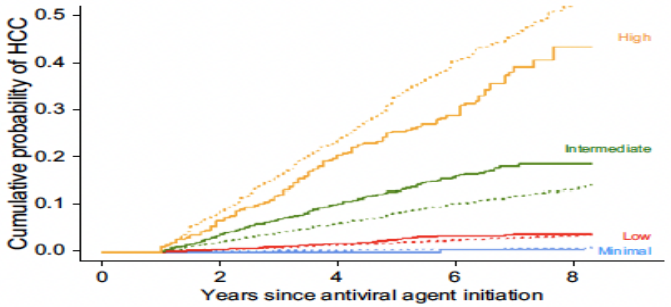
Room for improvement : risk stratification

PLAN-B model for the prediction of HCC in patients with chronic hepatitis B

- Machine learning approaches (gradient-boosting machine algorithm)
- Entecavir or tenofovir-treated

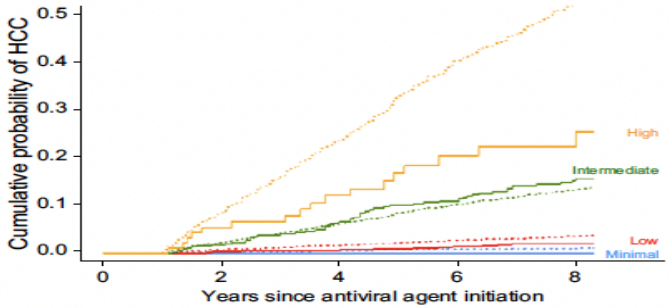


Derivation cohort
(Korea, n = 6,051)



Model	c-index	95% CI		p
		Lower	Upper	
PLAN-B	0.79	0.78	0.80	Ref.
PAGE-B	0.73	0.72	0.74	<0.001
mPAGE-B	0.75	0.74	0.76	0.004
REACH-B	0.63	0.61	0.64	<0.001
CU-HCC	0.72	0.71	0.73	<0.001

Korean validation cohort
(n = 5,817)

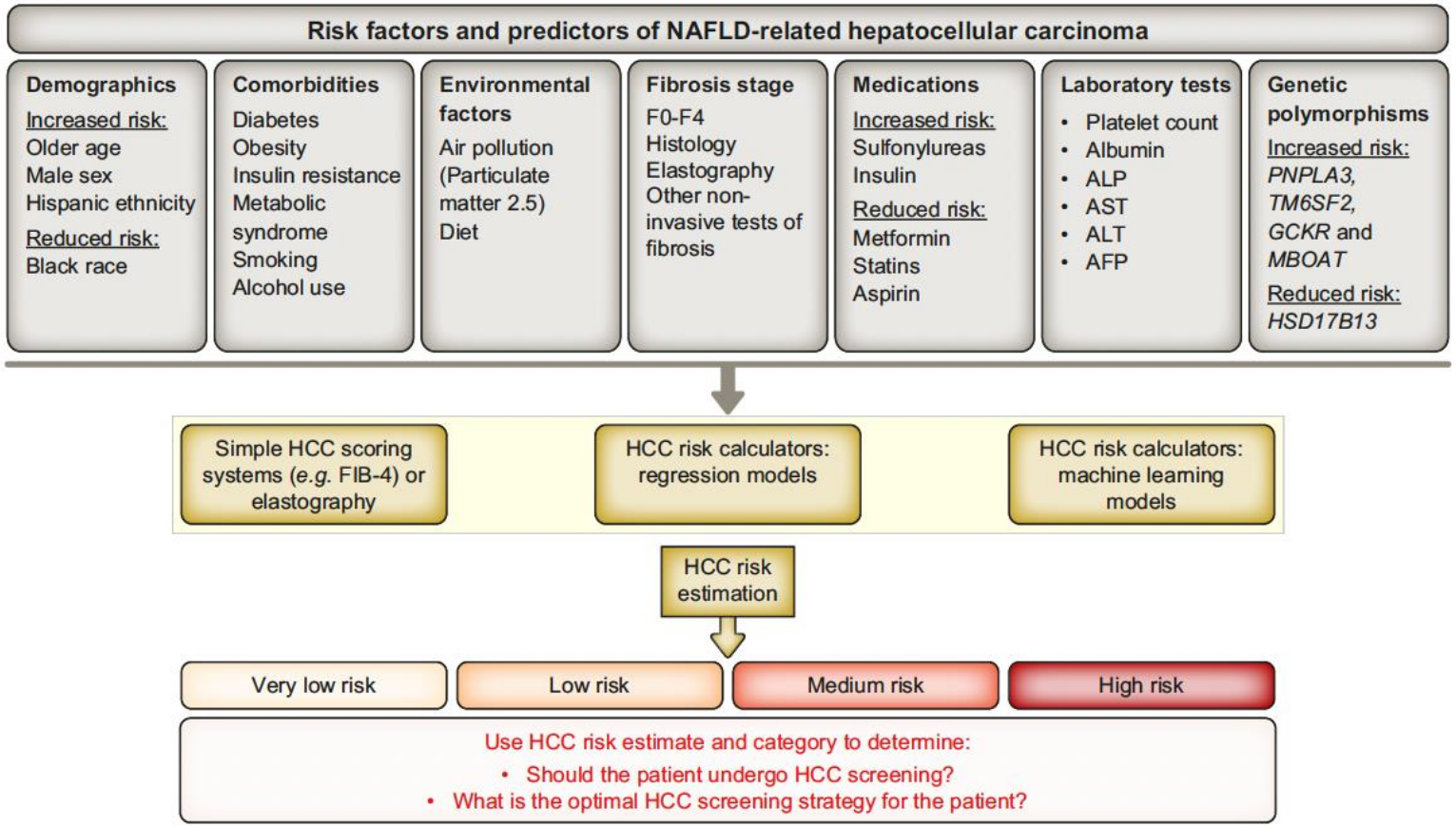


Model	c-index	95% CI		p
		Lower	Upper	
PLAN-B	0.81	0.79	0.83	Ref.
PAGE-B	0.75	0.73	0.77	<0.001
mPAGE-B	0.80	0.79	0.82	0.424
REACH-B	0.57	0.54	0.59	<0.001
CU-HCC	0.76	0.74	0.78	0.002

Caucasian validation cohort
(n = 1,640)

Kim et al J Hepatol 2021

Room for improvement: risk stratification



Nuevas perspectivas para el cribado

Combinaciones de parámetros clínicos y serológicos

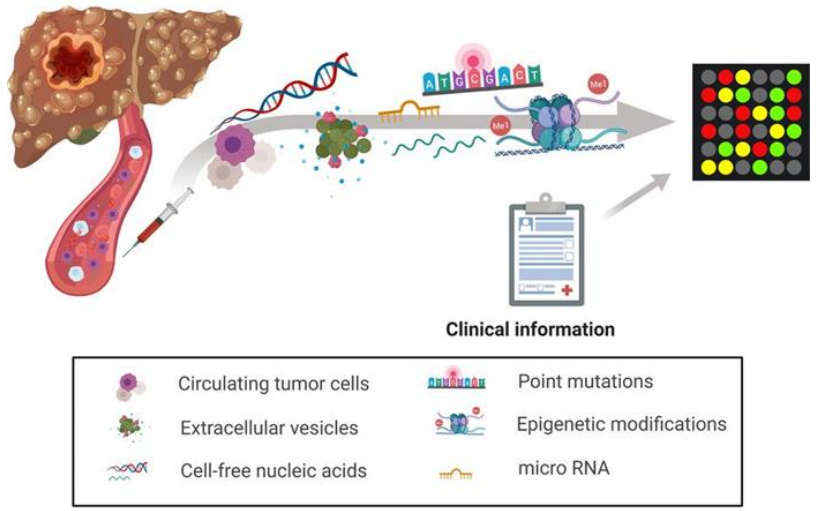
GALAD (Gender, **A**ge, **A**FP, AFP-**L**3,**D**CP)

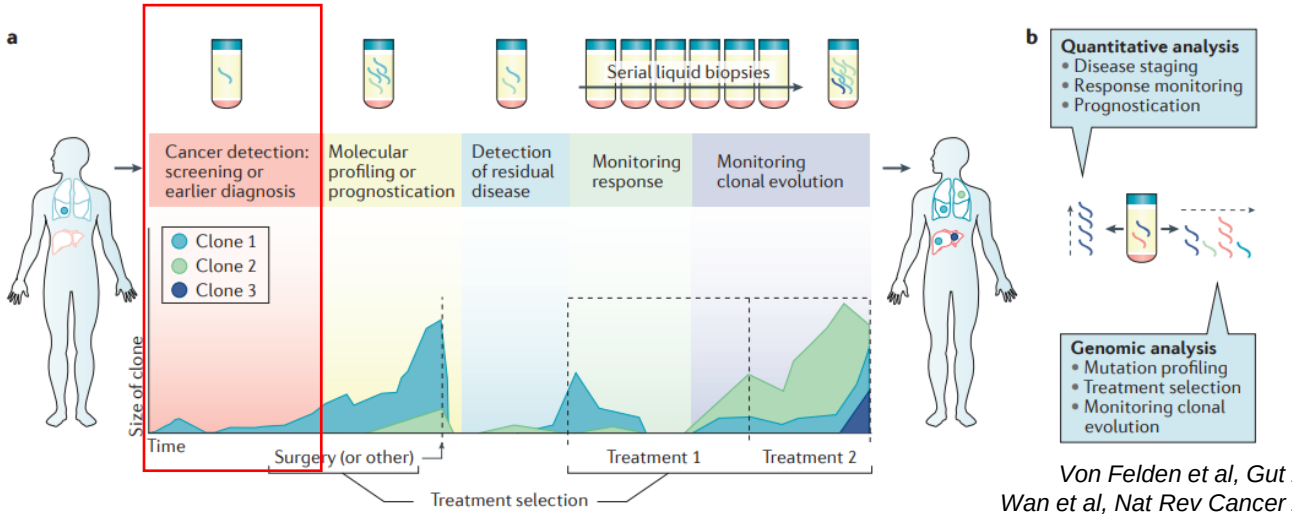
BALAD (Bilirrubina**, A**lbumina**,** AFP-**L3, A**FP, **D**CP**)**

BALAD-2

GALADUS (GALAD**+US)**

Biopsia líquida

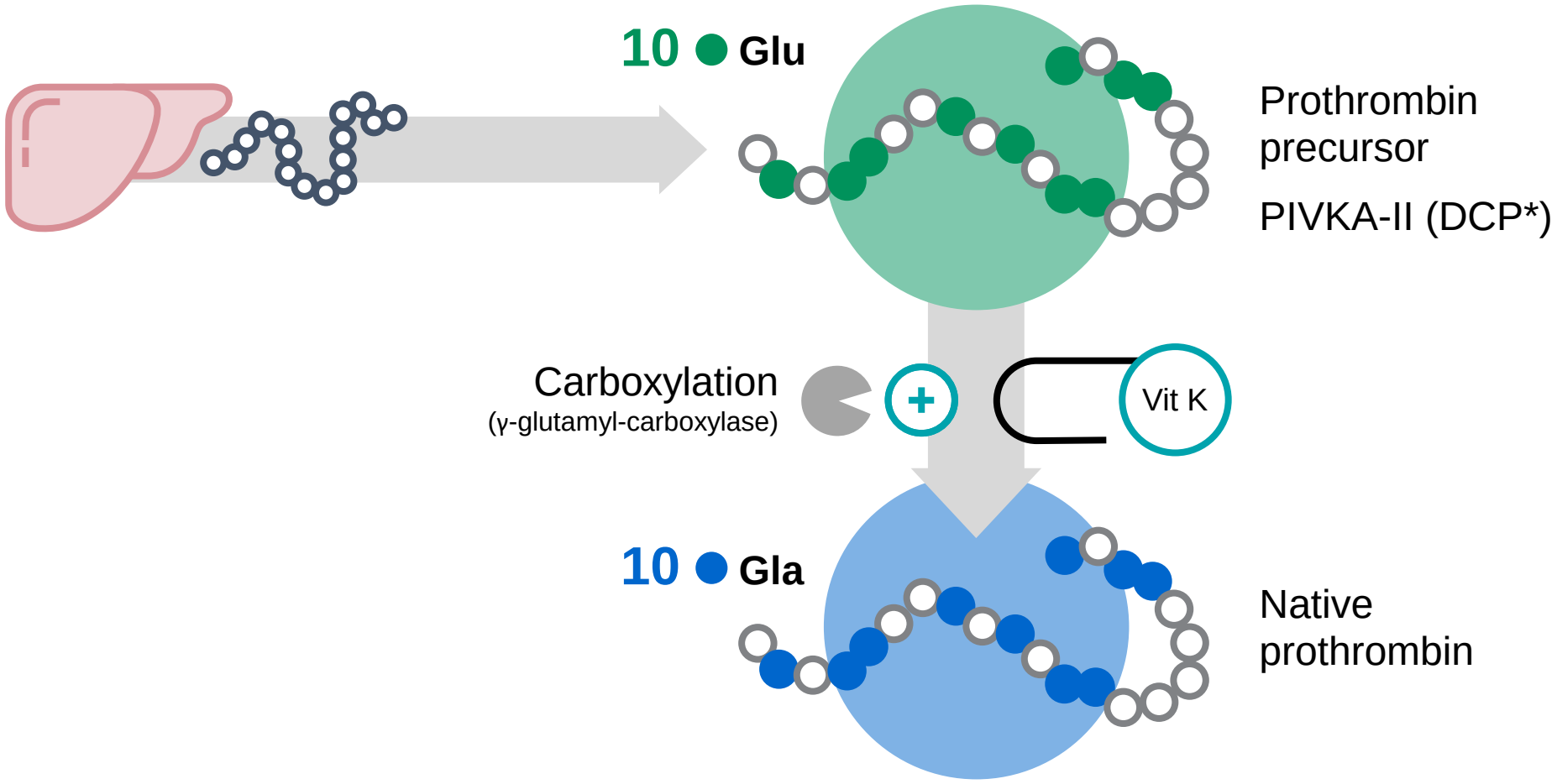




Von Felden et al, Gut 2020
Wan et al, Nat Rev Cancer 2017
Tzartzena, K et al, Gastroenterology 2018
Atiq O, et al. Hepatology 2017
Chang TS, et al. Am J Gastroenterol 2015

What is PIVKA-II?

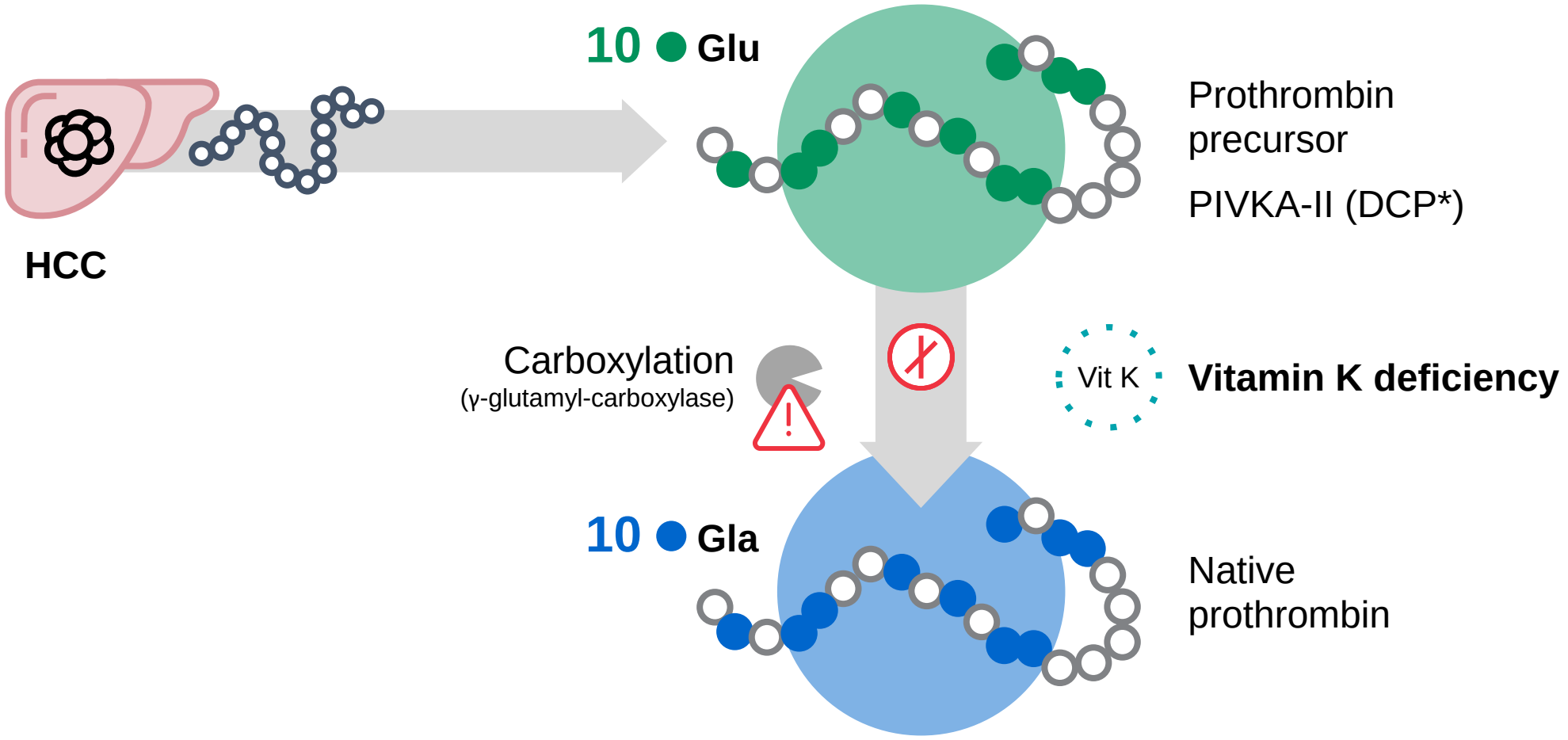
Normal process



Liebmann, H.A. et al. (1984). Des-gamma-carboxy (abnormal) prothrombin as a serum marker of primary hepatocellular carcinoma. N Eng J Med 310, 1427-1431.
Ono, M. et al. (1990). Measurement of immunoreactive prothrombin precursor and vitamin-K-dependent gamma-carboxylation in human hepatocellular carcinoma tissues: Decreased carboxylation of prothrombin precursor as a cause of des-gamma-carboxy prothrombin synthesis. Tumour Biol 11, 319-326.

What is PIVKA-II?

Vit K deficiency or HCC patient



Liebmann, H.A. et al. (1984). Des-gamma-carboxy (abnormal) prothrombin as a serum marker of primary hepatocellular carcinoma. N Eng J Med 310, 1427-1431.
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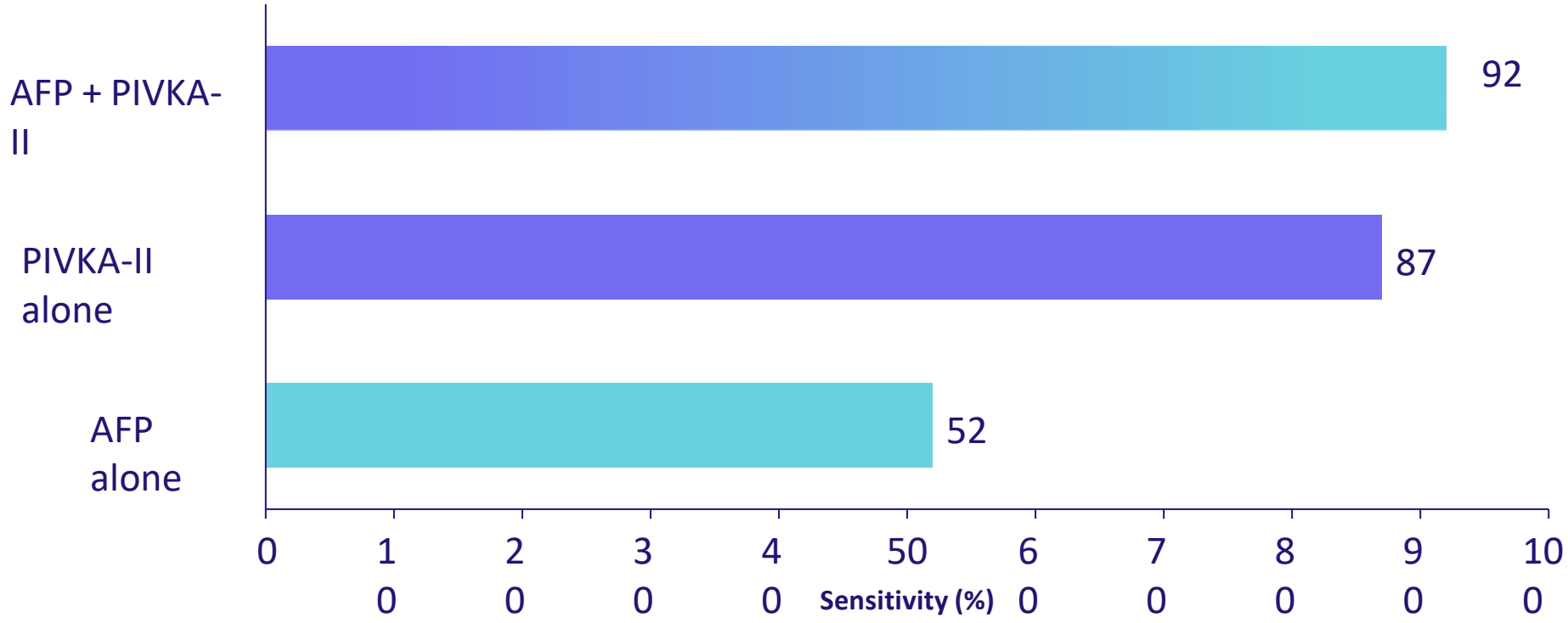
Combining AFP and PIVKA-II maximises sensitivity of HCC detection



Combining AFP and PIVKA-II may improve diagnostic performance

AFP and PIVKA-II are two of a number of biomarkers that could be used as a diagnostic aid.
Approved solutions may vary according to region.

1. Chan et al. ILCA 2020

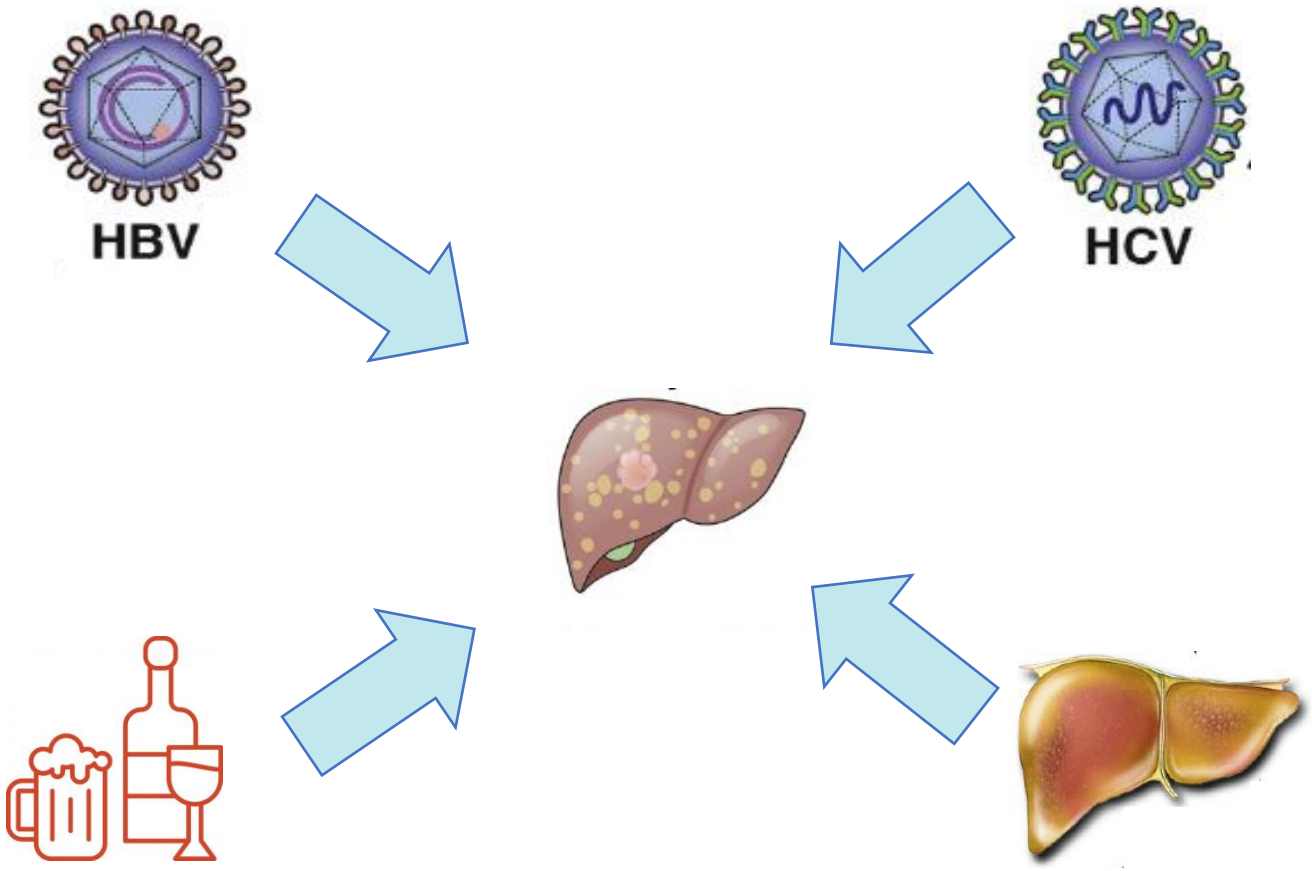
Circulating DNA based biomarkers for early HCC detection with regulatory approval

	Biomarker	Patients	Performance	Validation
HCCScreen (Genetron)	ctDNA mutations (HBV integrations, TP53, CTNNB1, AXIN1 and TERT)+AFP, DCP, age, gender	65 HCC training 331 HBsAg+ validation	Sens 85% Spec 93% Sens 100% Spec 94%	
Oncoguard (Exact Sciences)	cfDNA methylation markers (HOXA, TSPYL5 and B3GALT6), AFP, gender	156 HCC (50% early) 245 disease ethiology matched controls	82% early stage Sens Overall Sens 88% Spec 87%	NCT03628651
IvyGeneDx Liver Cancer Test (LAM)	cfDNA meth pattern+ age, gender, race and AJCC	1098 HCC 835 healthy T: 715 HCCvs560 V:383 HCCvs275	Training / Validation Sens 85.7% / 83.3% Spec 94.3% / 90.5% AUC 0.966 / 0.944	NCT0369460
HCCBlood test (Epigenomics AC)	SEPT9 promoter meth	98 HCC (33% BCLC A) vs cirrhotic	AUC 0.944 OR 6.3 AUC 0.930 OR 6.07 rep BCLC A : AUC 0.863	

Adapted from Grinspan, Semin Liver Dis 2022

Prevención primaria: Evitar los factores de riesgo

80-90% CHC se desarrollan sobre enfermedad hepática crónica



Prevención secundaria: Cribado de pacientes en riesgo

Población diana: alta incidencia y candidatos a tratamiento

Recommendations
• Cirrhotic patients, **Child–Pugh stage A and B**
• Cirrhotic patients, **Child–Pugh stage C awaiting LT**
• Non-cirrhotic HBV patients at intermediate or high risk of HCC* (according to PAGE-B† classes for Caucasian subjects, respectively 10–17 and ≥18 score points)
• Non-cirrhotic F3 patients, based on an individual risk assessment

Med Clin (Barc). 2021;156(9):463.e1–463.e30

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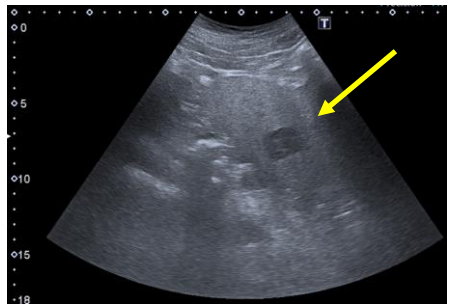
Conferencia de consenso

Diagnóstico y tratamiento del carcinoma hepatocelular. Actualización del documento de consenso de la AEEH, AEC, SEOM, SERAM, SERVEI y SETH

María Reig[a,b], Alejandro Forner[a,b], Matías A. Ávila[b,c], Carmen Ayuso[b,d], Beatriz Mínguez[b,e], María Varela[f], Itxarone Bilbao[b,g], José Ignacio Bilbao[h], Marta Burrel[d], Javier Bustamante[i], Joana Ferrer[j], Miguel Ángel Gómez[k], Josep María Llovet[l], Manuel De la Mata[b,m], Ana Matilla[b,n], Fernando Pardo[o], Miguel A. Pastrana[p], Manuel Rodríguez-Perálvarez[b,m], Josep Tabernero[q], José Urbano[r], Ruth Vera[s], Bruno Sangro[b,t,*] y Jordi Bruix[a,b,*]

Ecografía semestral



Explorador dependiente
Dificultades técnicas y anatómicas

- Paciente con cirrosis: cribado
- Técnica: ecografía abdominal realizada por personal experto
- No se recomienda el uso de AFP
- Ecografía semestral
- EHGNA sin cirrosis y pacientes VHC en RVS sin fibrosis avanzada NO hay datos

EASL Clinical Practice Guidelines. J Hepatol 2018
Reig M et al Med Clin (Barc) 2021

AASLD Guidelines

7. Patients at high risk of developing HCC (see **Table 1**) should be entered into HCC surveillance programs, provided they would be candidates for HCC treatment (**Level 2, Strong Recommendation**).

    a. Patients with Child-Turcotte-Pugh class C cirrhosis should not be enrolled in surveillance programs unless they are eligible for liver transplantation (**Level 3, Strong Recommendation**).

    b. All patients listed for liver transplantation should undergo semiannual HCC surveillance because identification of early-stage HCC changes priority for transplantation (**Level 3, Strong Recommendation**).

    c. AASLD recommends against HCC surveillance in patients with life-limiting comorbid conditions that cannot be remedied by liver transplantation or other directed therapies (**Level 5, Strong Recommendation**).

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AASLD Guidelines

8. AASLD recommends against routine use of HCC surveillance in patients with HCV infection post-SVR with advanced fibrosis but without cirrhosis (**Level 3, Weak Recommendation**).
9. AASLD recommends against routine use of HCC surveillance in patients with NAFLD who have advanced fibrosis but without cirrhosis (**Level 3, Weak Recommendation**).
10. HCC surveillance should be performed using ultrasound and AFP at semiannual (approximately every 6 months) intervals (**Level 2, Strong Recommendation**).
    a. AASLD recommends use of interventions such as best practice alerts or outreach programs to increase HCC surveillance adherence given the underuse of surveillance in clinical practice (**Level 2, Strong Recommendation**).
11. AASLD does not recommend routine use of CT- or MRI-based imaging and tumor biomarkers, outside of AFP, for HCC surveillance in at-risk patients with cirrhosis or chronic HBV (**Level 5, Weak Recommendation**).
    a. Alternative imaging modalities, such as contrast-enhanced MRI, may be considered for HCC surveillance in select patients in whom US-based surveillance is suboptimal (**Level 3, Weak Recommendation**).

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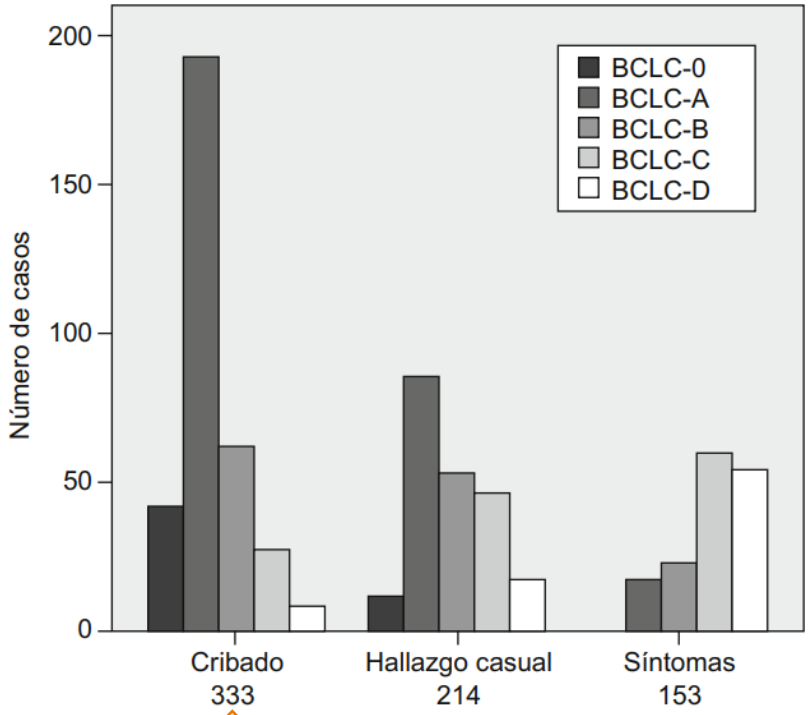
Cribado en España: Datos de los registros HCC AEEH

registroHCC AEEH

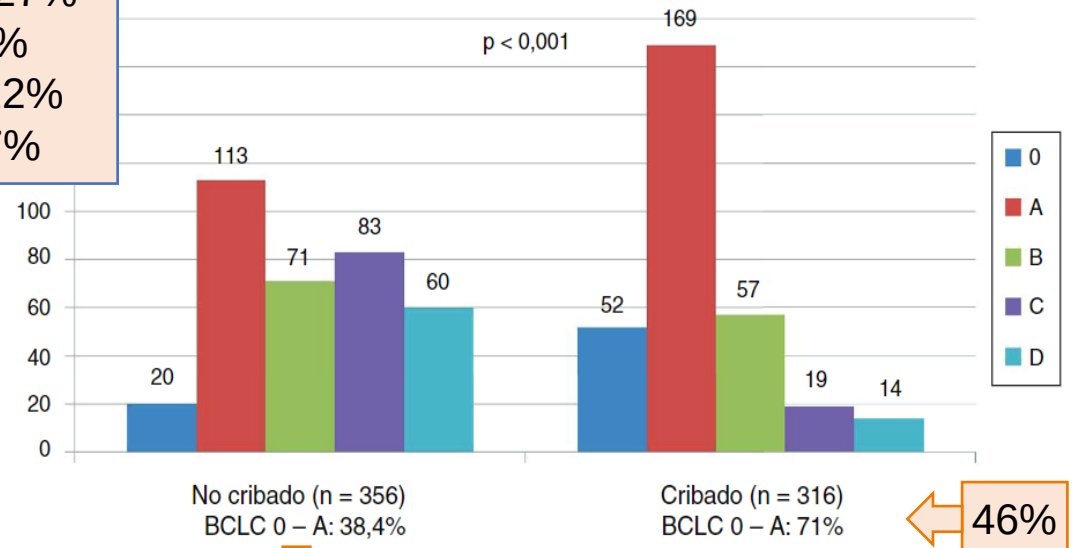
Primer Registro CHC
(Oct 2008-En 2009)
(n=649)



51%

En otros paises occidentales
Francia 28%
Holanda 27%
UK 26%
Suecia 22%
USA 17%

Segundo Registro CHC
(Oct 2014-En 2015)
(n=686)



46%

76% desconocimiento enfermedad hepática
18% mala adherencia por parte del paciente
6% no fue indicada por su especialista

Datos preliminares provisionales del tercer registro CHC: 46,9% de diagnostico en cribado

Varela M et al Med Clin 2010
Rodriguez de Lope C et al Med Clin C 2017

More than 20% of patients with cirrhosis do not receive semi-annual HCC surveillance as recommended[1]

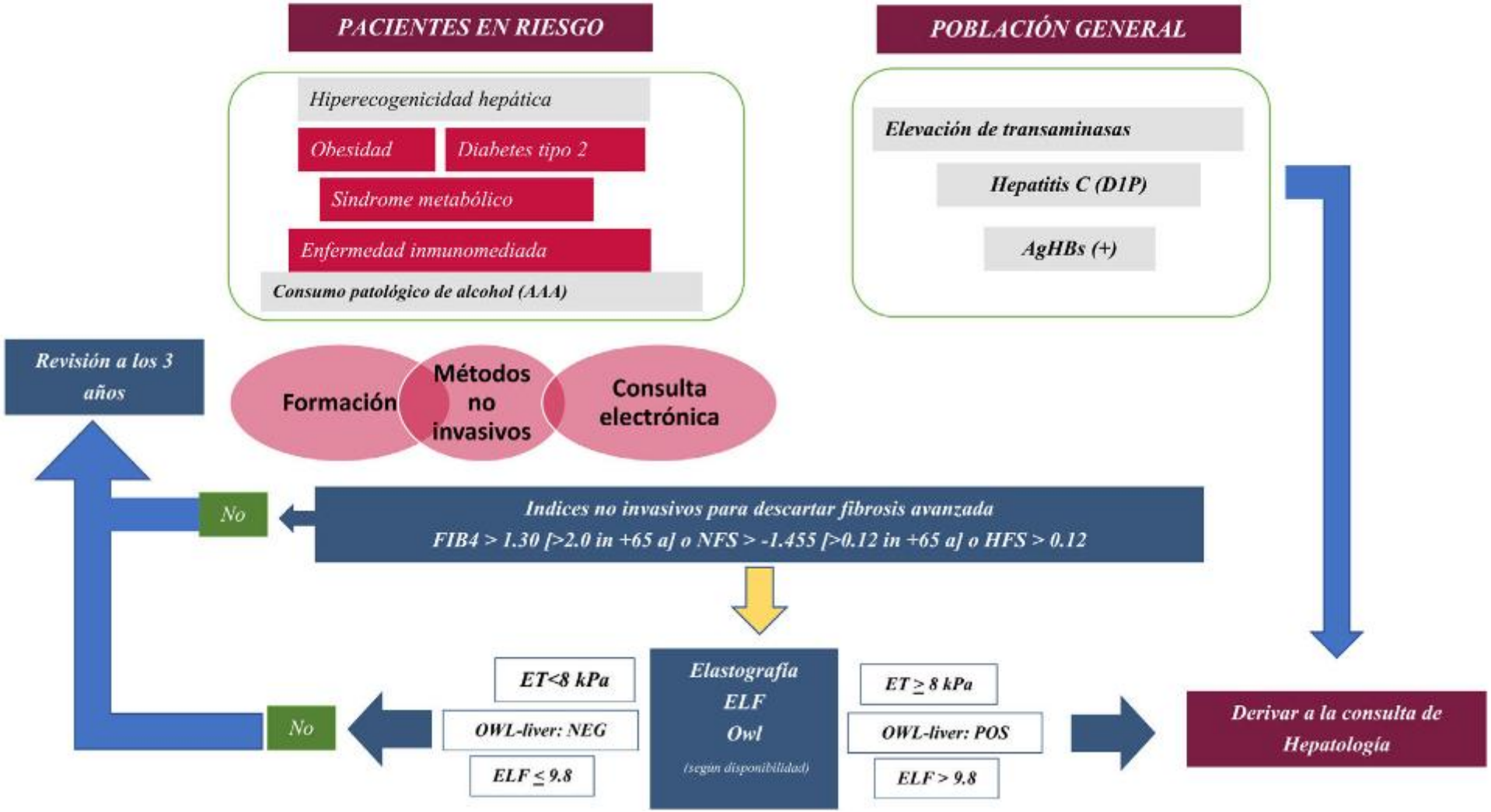
Barriers to HCC surveillance, according to patient, clinician and health system

Patient factors	Clinician factors	Health system factors
• Poor knowledge of surveillance benefit	• Suboptimal knowledge on guidelines	• Racial/social/economic disparities in surveillance rates
• Scheduling difficulties	• Limited clinic time	• Lack of automated screening processes
• Costs	• Longer US lead time associated with lower completion rates	• Speciality care not widely available
• Getting to/from imaging centres		

1. Singal et al. Clin Gastroenterol Hepatol 2020
2. Deng and Mehta. Dig Dis Sci 2020

Consenso AEEH para detección de pacientes con hepatopatía crónica

Algoritmo de detección y derivación de enfermedades hepáticas prevalentes



Romero Gómez M et al, Gastroenterol Hepatol 2022

How can we improve HCC surveillance?

Increasing surveillance

Promoting education

- Patient education
- Practitioner training
- Enlisting primary care providers

Improving compliance

- Systems-level interventions
- Dedicated clinical pathways
- Clinical reminder systems
- Navigation programmes
- Mailed outreach

Recommended semi-annual US surveillance

Personalized screening

Risk stratification

Predictive biomarkers

Machine learning

Low HCC risk

Moderate/high HCC risk

Screening with contrast-enhanced imaging

+

Early diagnosis biomarkers

1. Singal et al. J Hepatol 2020

Precision Medicine in HCC screening