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Liver Cancer

The risk of hepatocellular carcinoma decreases after NAs treatment in Caucasians with chronic hepatitis B: The Role of PAGE-B

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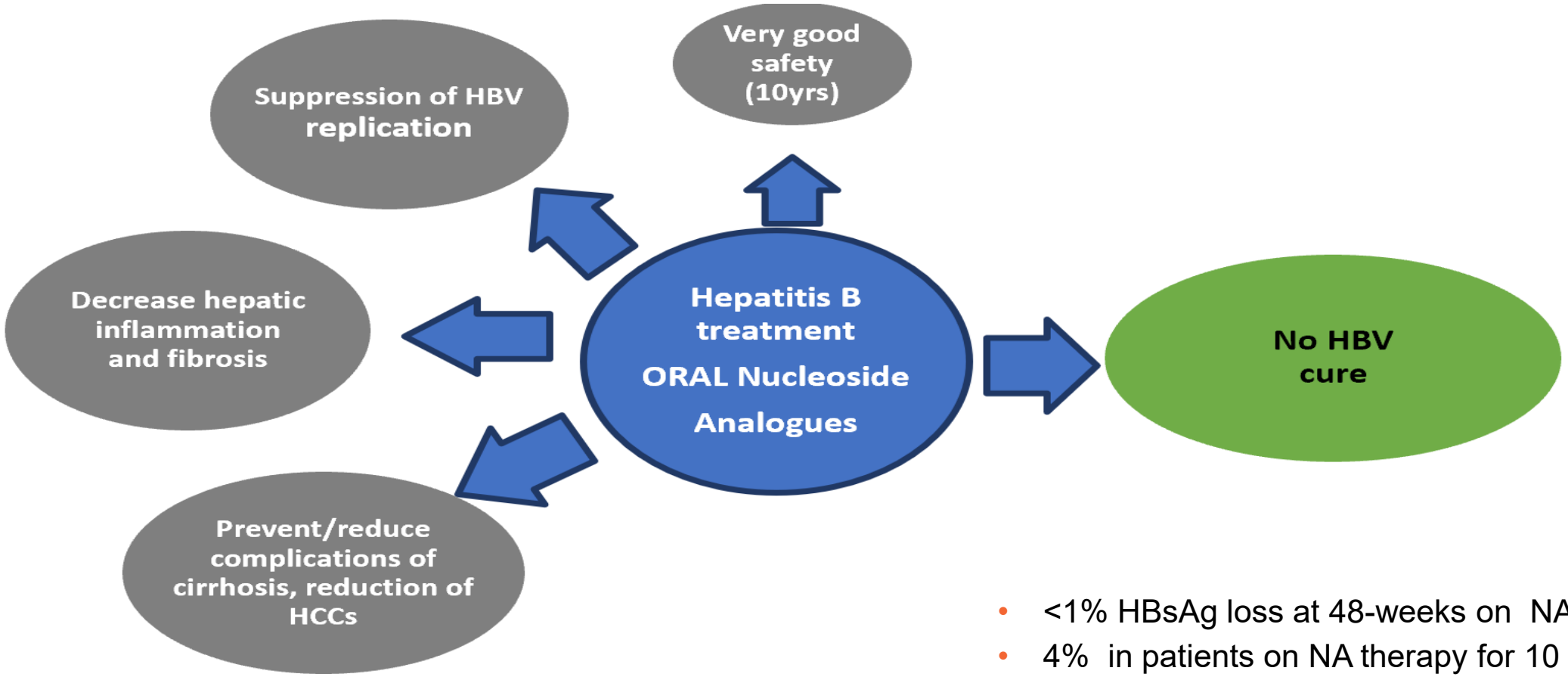
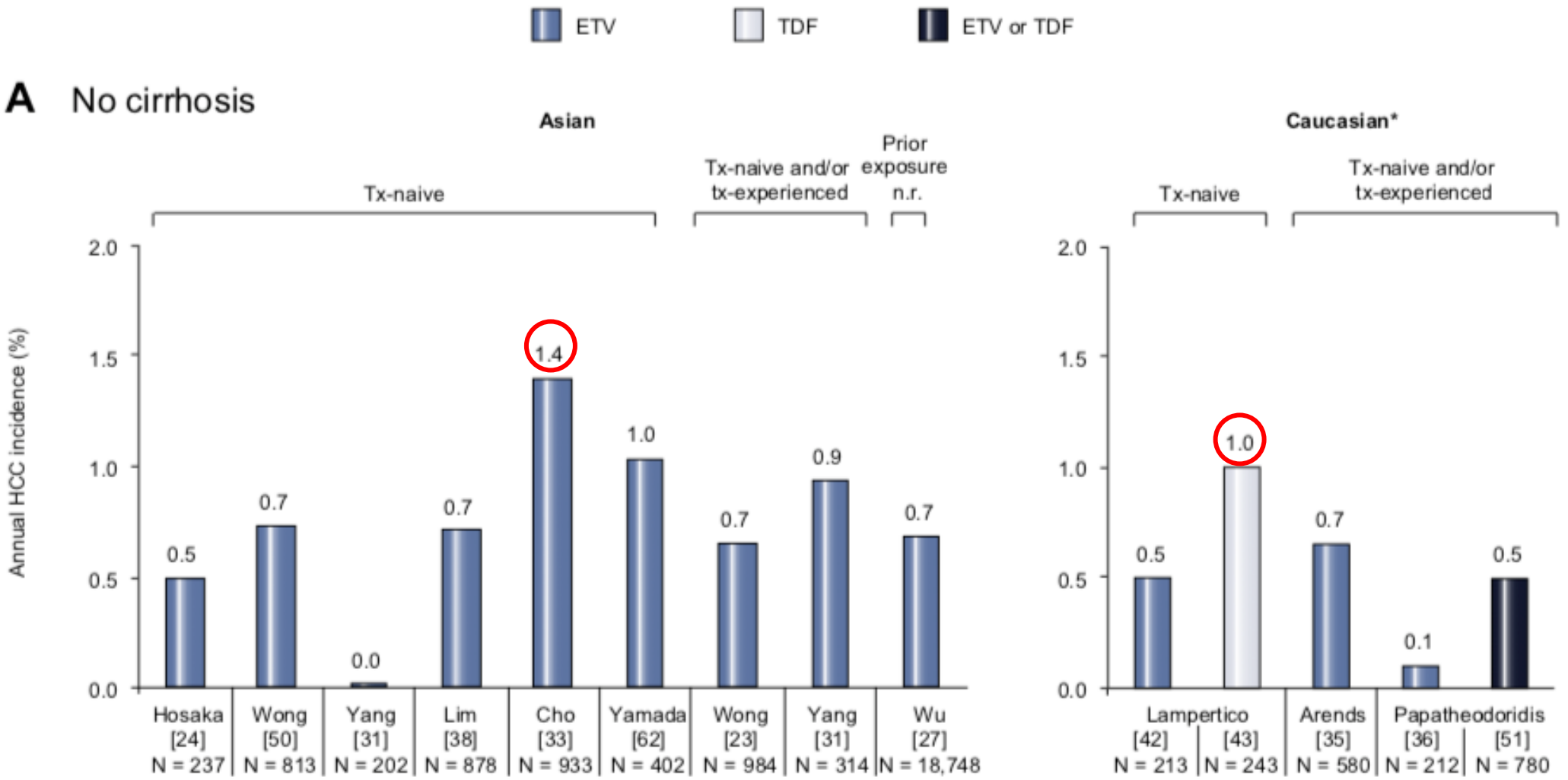
Achievements with NAs in the Treatment of Hepatitis B



- <1% HBsAg loss at 48-weeks on NAs therapy[1]
- 4% in patients on NA therapy for 10 years[2]

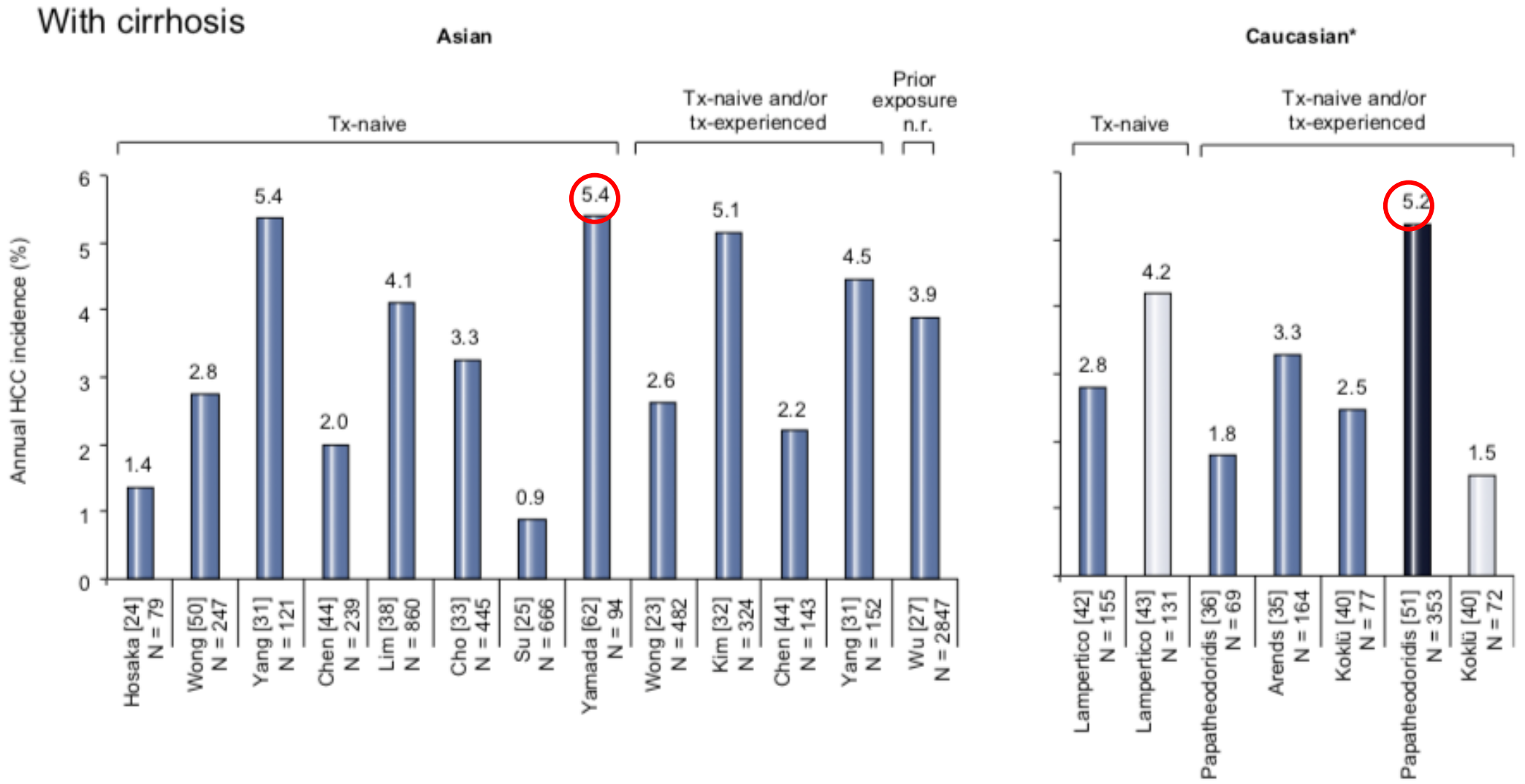
1. Marcellin P, et al. *Liver Int*. 2019;39(10):1868–1875; 2 Slaets L, et al. *Gastroenterol Hepatol.* 2020;2(3):106–116

Annual HCC Incidence Rates with ETV or TDF in Chronic Hepatitis B *Without* Cirrhosis



Reviewed by Papatheodoridis G et al J Hepatology 2015

Annual HCC Incidence Rates with ETV or TDF in Chronic Hepatitis B With Cirrhosis



Papatheodoridis G et al J Hepatol 2015

Risk predicting scores of HCC development in CHB patients

Predicting scores	Predictors	5-year AUROC to predict HCC risk
PAGE-B[122]	Age, male, platelet	0.82
mPAGE-B[123]	Age, male, platelet, albumin	0.82
HCC-RESCUE[124]	Age, male, cirrhosis	0.77
APA-B[125]	Age, platelet, alpha-fetoprotein	0.827
CAMD[126]	Age, male, cirrhosis, diabetes	0.76
AASL-HCC[127]	Age, male, albumin, cirrhosis	0.802
REAL-B[128]	Age, male, alcohol use, diabetes, cirrhosis, platelet, alpha- fetoprotein	0.80

PAGE-B score is the only one developed in Caucasian patients

Lin CL. Clin Mol Hepatol. 2023

Research Article

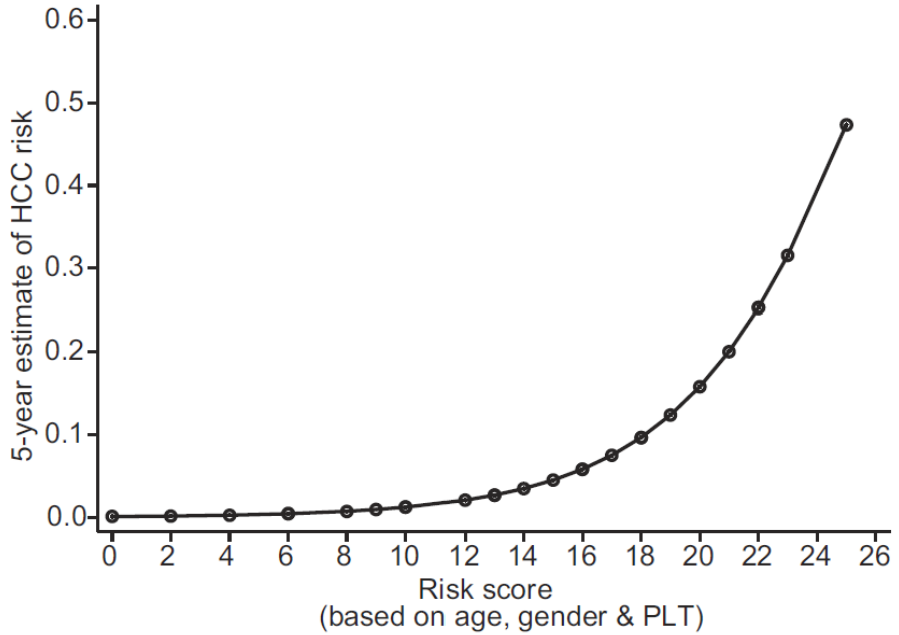
JOURNAL OF HEPATOLOGY

PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy

George Papatheodoridis[1,2,*], George Dalekos[3], Vana Sypsa[4], Cihan Yurdaydin[5], Maria Buti[6], John Goulis[7], Jose Luis Calleja[8], Heng Chi[9], Spilios Manolakopoulos[2], Giampaolo Mangia[10], Nikolaos Gatselis[3], Onur Keskin[5], Savvoula Savvidou[7], Juan de la Revilla[8], Bettina E. Hansen[9], Ioannis Vlachogiannakos[1], Kostantinos Galanis[3], Ramazan Idilman[5], Massimo Colombo[10], Rafael Esteban[6], Harry L.A. Janssen[9,11], Pietro Lampertico[10]

1815 adult Caucasians with CHB
no HCC at baseline
ETV/TDF > 12 months
derivation dataset, n = 1325)
HCC risk score: Multivariable Cox models
validation dataset, n = 490
Points based in Patients´Baseline Factors

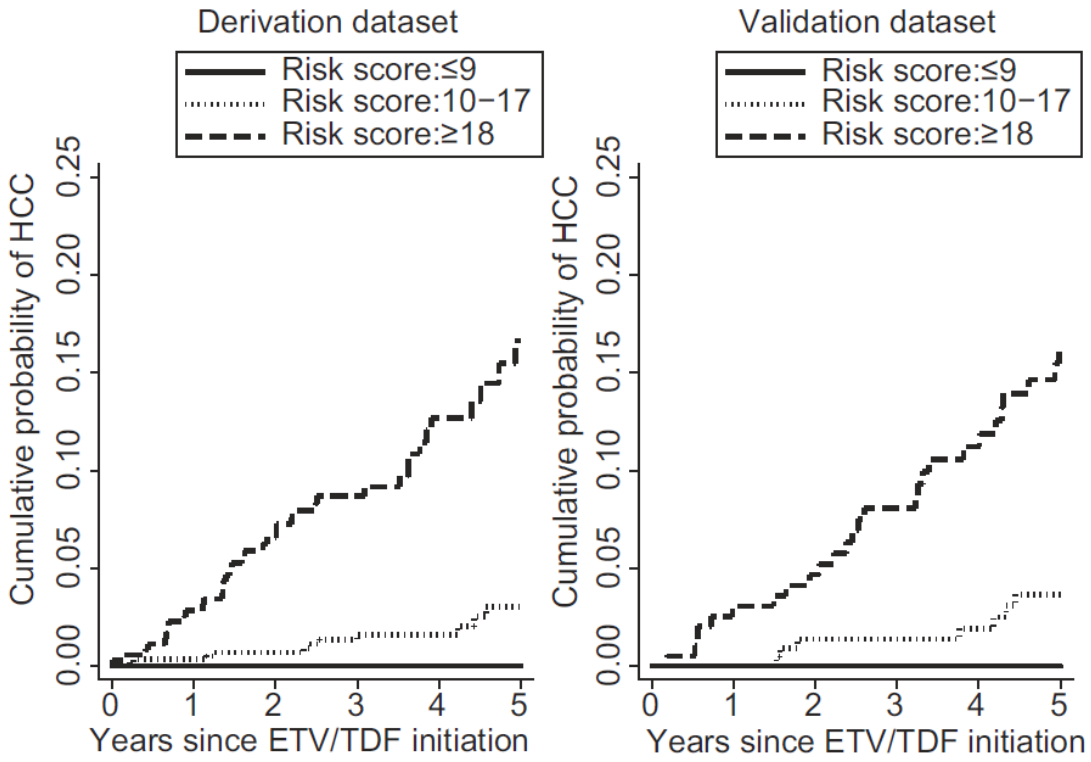
Age (years)	Gender	Platelets (/mm^3)
16-29: 0	Female: 0	≥200,000: 0
30-39: 2	Male: 6	100,000-199,999: 6
40-49: 4		<100,000: 9
50-59: 6		
60-69: 8		
≥70: 10		



5-year cumulative HCC incidence rates were 5.7%

Papatheodoridis G. J Hepatol. 2016

Cumulative probability of HCC in the derivation and validation dataset of patients treated with ETV or TDF according to their PAGE-B risk scores.



Accuracy for prediction of HCC within the first 5 years of NAs using the cut-off point of >10 in the PAGE-B risk score.

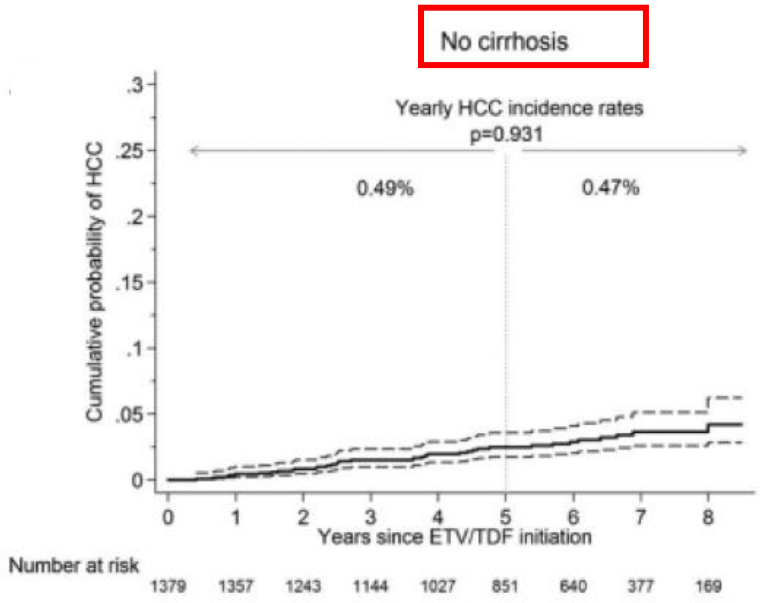
	PAGE-B risk score >10	
	Derivation cohort (N = 1264)	Validation cohort (N = 484)
Sensitivity	100%	100%
Specificity	41.2%	19.6%
Positive predictive value	9.8%	10.3%
Negative predictive value	100%	100%

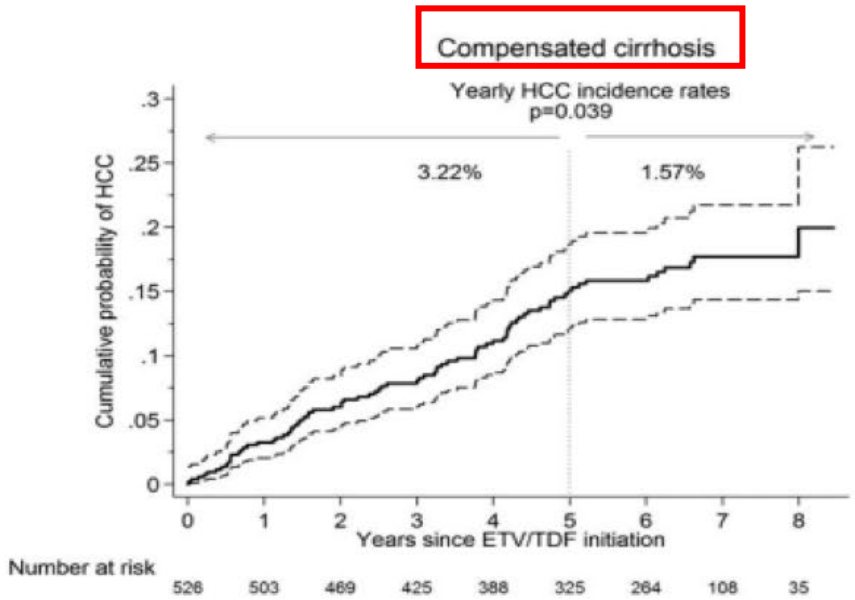
PAGE-B represents a simple and reliable score for prediction of the 5-year HCC risk in Caucasian CHB patients under NAs

Papatheodoridis G. J Hepatol. 2016

HCC Prevented Beyond Five Years of NA Therapy in Cirrhosis Only. PAGE-B Cohort

➢ **Cohort** :10-centers,1,951 adult HCC-free Caucasians on ETV/TDF for > 1 year



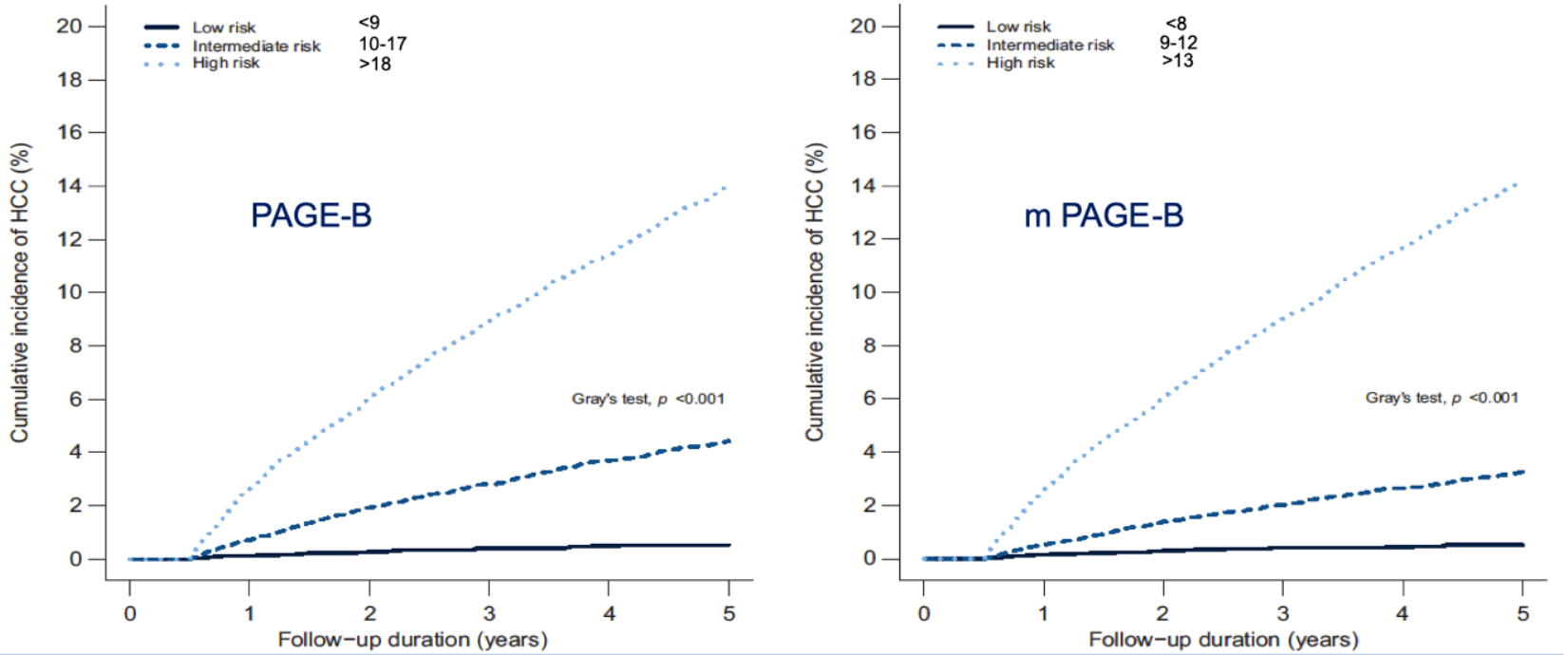


➢ **Late HCC predictors** : older age (especially ≥50 years), lower platelets and liver stiffness ≥12 kPa at year 5

Papatheodoridis G et al Hepatology 2017

PAGE B Predicts HCC in Asians with NA Suppressed Chronic Hepatitis B. Hong Kong Study

With either one of the low risk scores 9,417 (29.3%) patients classified as low risk 43 (0.5%) developed HCC in 5 yrs



N° at risk												
Low risk	7,198	6,448	5,177	4,251	3,378	2,704	7,746	7,020	5,824	4,874	3,981	3,231
Intermediate risk	15,212	13,804	11,239	9,387	7,663	6,098	12,643	11,579	9,531	7,954	6,489	5,179
High risk	9,740	8,676	6,961	5,750	4,597	3,555	11,761	10,329	8,022	6,560	5,168	3,947

Yip TCF et al J Hepatol 2020

Surveillance in patients at high risk of HCC

Recommendations

	Level of evidence	Grade of recommendation
• Cirrhotic patients, **Child–Pugh stage A and B**	Low	Strong
• Cirrhotic patients, **Child–Pugh stage C awaiting LT**	Low	Strong
• 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)	Low	Weak
• Non-cirrhotic F3 patients, based on an individual risk assessment	Low	Weak
Role of **surveillance for patients with NAFLD** without cirrhosis is **unclear**	Low	

*Patients at low HCC risk left untreated for HBV and without regular 6-month surveillance must be reassessed at latest on a yearly basis to verify progression of HCC risk.
†PAGE-B score is based on decade of age (16–29 = 0, 30–39 = 2, 40–49 = 4, 50–59 = 6, 60–69 = 8, ≥70=10), gender (M = 6, F = 0) and platelet count (≥200,000/µl = 0, 100,000–199,999µl = 1, <100,000 = 2): a total sum of ≤9 is considered at low risk of HCC (almost 0% HCC at 5 years) a score of 10–17 at intermediate risk (3% incidence HCC at 5 years) and ≥18 is at high risk (17% HCC at 5 years)

EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

EASL™ The Home of Hepatology

mPAGE-B score for Asian NAs treated patients

mPAGE-B

The simple formula of the modified PAGE-B score

Age (years)	Risk score	Gender	Risk score	Platelets ($x10^9$/L)	Risk score	Albumin (g/dl)	Risk score
<30	0	Female	0	>250	0	≥4.0	0
30-39	3	Male	2	200-250	2	3.5-4.0	1
40-49	5			150-200	3	3.0-3.5	2
50-59	7			100-150	4	<3.0	3
60-69	9			<100	5		
≥70	11						

The modified PAGE-B score stratifies the HCC risk in Asian patients with chronic hepatitis B under antiviral therapy

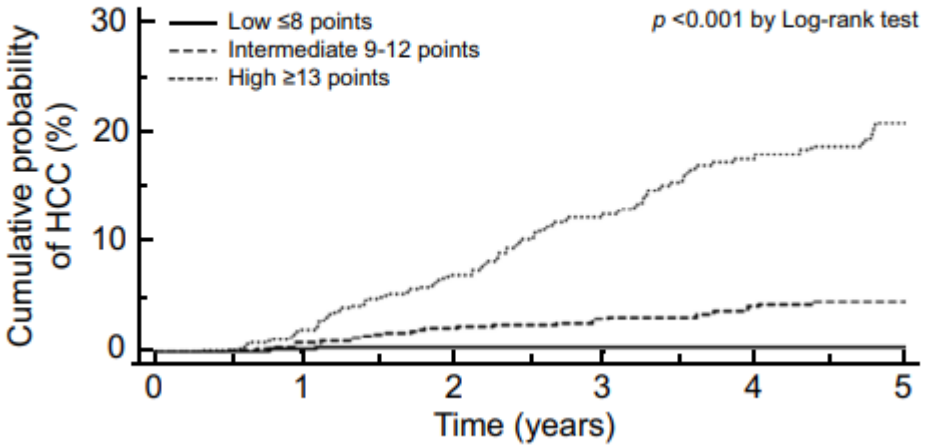
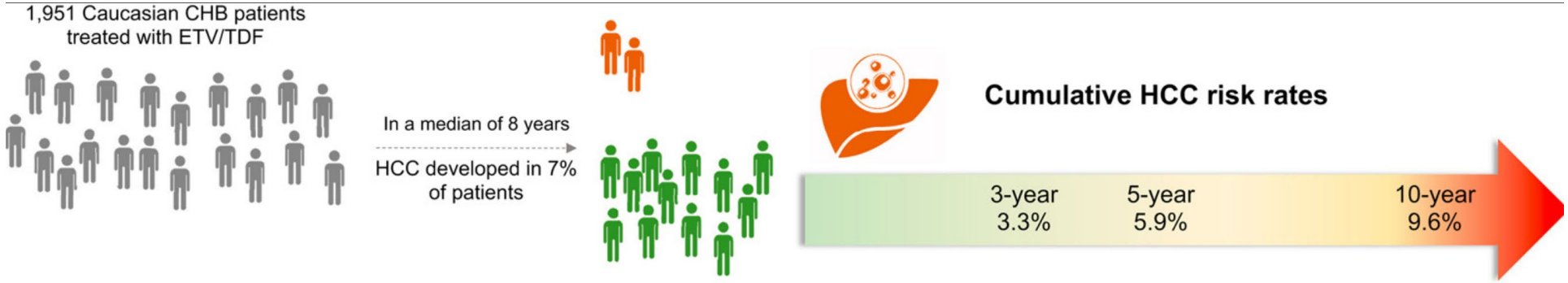


Table 4. Comparison of predictive performance for HCC development within five years.

Prediction model	Time-dependent AUROC (95% CI)
Modified PAGE-B	0.82 (0.76–0.88)
PAGE-B	0.72 (0.65–0.78)

Kim JH. J Hepatol. 2018

Predictive performance of newer Asian HCC risk scores in treated Caucasians with CHB

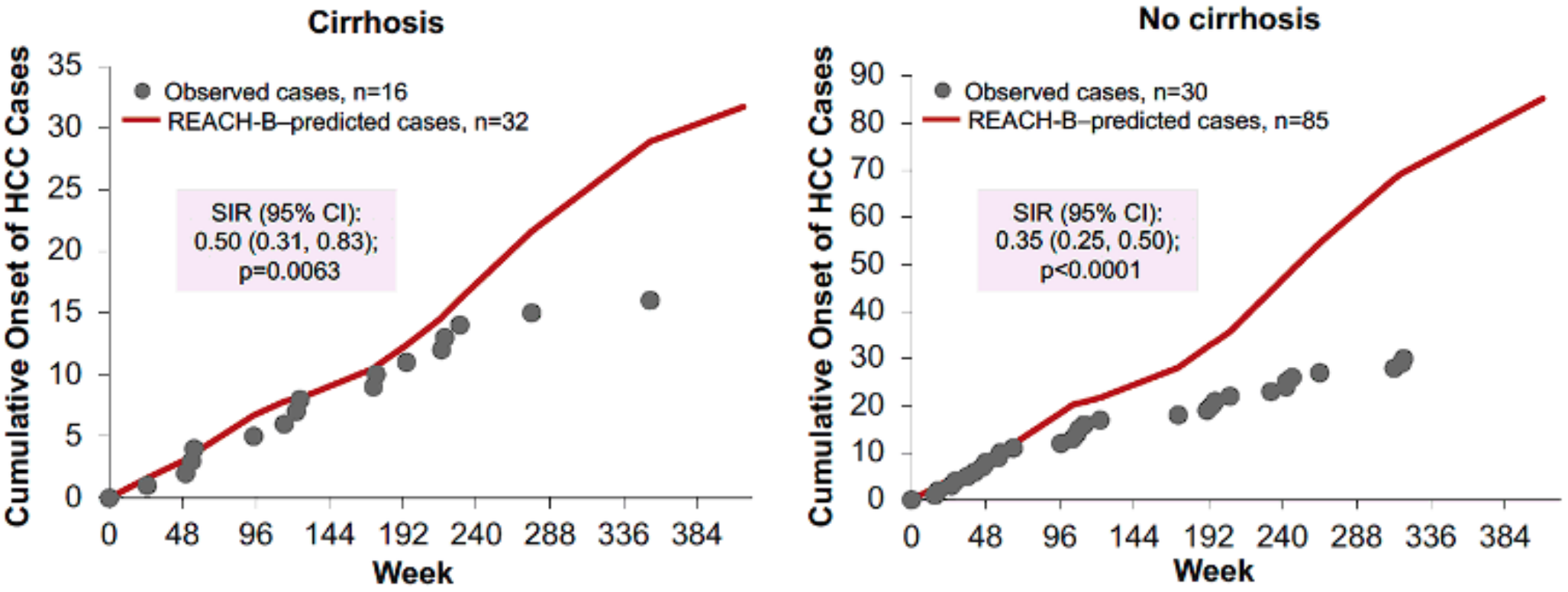


HCC risk score	Low/High-risk group cut-off	AUROC, c-statistic (95% CI)	Sensitivity, %	NPV, %
At baseline		**5-year HCC prediction**		
PAGE-B	10/18	0.80 (0.76, 0.83)	99.3%	99.8%
HCC-Rescue	65/85	0.81 (0.78, 0.84)	97.2%	99.5%
CAMD	8/14	0.79 (0.74, 0.83)	100%	100%
mPAGE-B	9/13	0.82 (0.78, 0.85)	97.8%	99.3%
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 Hepatol 2021

Can HCC risk scores applied to patients under treatment with Tenofovir Alafenanide?

Observed vs. Predicted HCC Cases by REACH-B Analysis over 8 Years,



SIR is Standardized Incidence Ratio of observed cases/predicted cases as determined by REACH-B.
CI, confidence interval; HCC, hepatocellular carcinoma; REACH-B, Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B; SIR, standardized incidence ratio

Kim R et al. EASL 2024

Shifts in HCC Risk from Baseline to Year 8 (Week 384), Pooled Analysis Using mPAGE-B Model

		Baseline		
	n (%)[a]	Low risk (n=1,251)	Medium risk (n=810)	High risk (n=208)
Year 8	Low risk	749 (97)	157 (26)	3 (2)
	Medium risk	26 (3)	427 (72)	69 (51)
	High risk	0	10 (2)	64 (47)
	Missing[b], n	476	216	72

Most patients who were low- or medium-risk at baseline either remained at those risk categories or shifted to a lower risk group by Week 384.
Of the patients who were high-risk at baseline, most shifted to medium or low-risk by Week 384

Kim R et al. EASL 2024

EASL Recommendations for Surveillance in Nas Suppressed HBV

Patients under effective long-term NA therapy should remain under surveillance for HCC. (Evidence level II-2, grade of recommendation 1)

HCC surveillance is mandatory for all patients with cirrhosis as well as those with moderate or high HCC risk scores at the onset of NA therapy. (Evidence level II-2, grade of recommendation 1)

EASL CPG HBV J Hepatol 2017

Incidence of HCC in patients with a PAGE-B score > 10

Cohort ANRS C022 HEPATHER & SNDS, prospective follow up median 99 months (89-109)

1 935 patients with advanced fibrosis and a PAGE-B score < and > 10 or without advanced fibrosis and PAGE-B score> 10

	Group 1 Advanced Fibrosis PAGE-B < 10 (n = 76)	Group 2 Advanced Fibrosis PAGE-B ≥ 10 (n = 343)	Group 3 NO Advanced Fibrosis PAGE-B ≥ 10 (n = 1 516)	p
Hepatic Decompensation, n (%)	0 (0 %)	3 (0,9 %)	8 (0,5 %)	**0,59**
Liver Transplantation, n (%)	0 (0 %)	4 (1,2 %)	0 (%)	**0,001**
Death, n (%)	4 (5,3 %)	51 (14,9 %)	76 (5 %)	**< 0,0001**
HCC, n (%) **Incidence /100 p-yr (IC 95%)**	**1 (1,3 %)** **0,17 (0,00-0,96)**	**31 (9 %)** **1,25 (0,85-1,77)**	**13 (0,9 %)** **0,11 (0,06-0,19)**	**< 0,0001**

Parlati L, , AASLD 2024,

HCC surveillance in clinical practice is suboptimal

Frequency of Surveillance according to Page B Group

Type of HCC Surveillance	**Total** n= 1 935	**Group 1** AF & PAGE B < 10 n = 76	**Group 2** AFF& PAGE-B ≥ 10 n = 343	**Group 3** NO AF&AGE-B ≥ 10 n = 1 516	**p**
Every 6 monts (Su-R6)	31 (1,6 %)	2 (2,6 %)	14 (4,1 %)	15 (1 %)	
Every 12 monts (Su-R12)	389 (20,1 %)	19 (25 %)	141 (41,1 %)	229 (15,1 %)	< 0,0001
Irregular (Su-I)	1 432 (74 %)	51 (67,1 %)	183 (53,3 %)	1 198 (79 %)	
None (Su0)	83 (4,3 %)	4 (5,3 %)	5 (1,5 %)	74 (4,9 %)	

HCC detected by frequency of Surveillance

	Overall (n = 1 852)	**Every 6 mo** (n = 31)	**Every 12 mo** (n = 389)	**Irregular** (n = 1 432)
HCC, n (%)	45 (2,3 %)	10 (22,2 %)	23 (51,1 %)	12 (26,7 %)

73,3 %

Therapy of HCC in function of Surveillance

HCC Therapy	**Total** (n = 45)	**Every 6 mo** (= 10)	**Every 12 mo** (n = 23)	**Irregular** (n = 12)	**p**
Therapy, n (%)					
- Curative	18 (54,6 %)	6 (66,7 %)	9 (56,3 %)	3 (37,5 %)	0,052
- Paliative	15 (45,5 %)	3 (33,3 %)	7 (43,8 %)	5 (62,5 %)	

Curative = 60 %
Paiative = 40 %

Parlati L,et al AASLD 2024,

Clinical utility of HCC risk scores in chronic hepatitis B

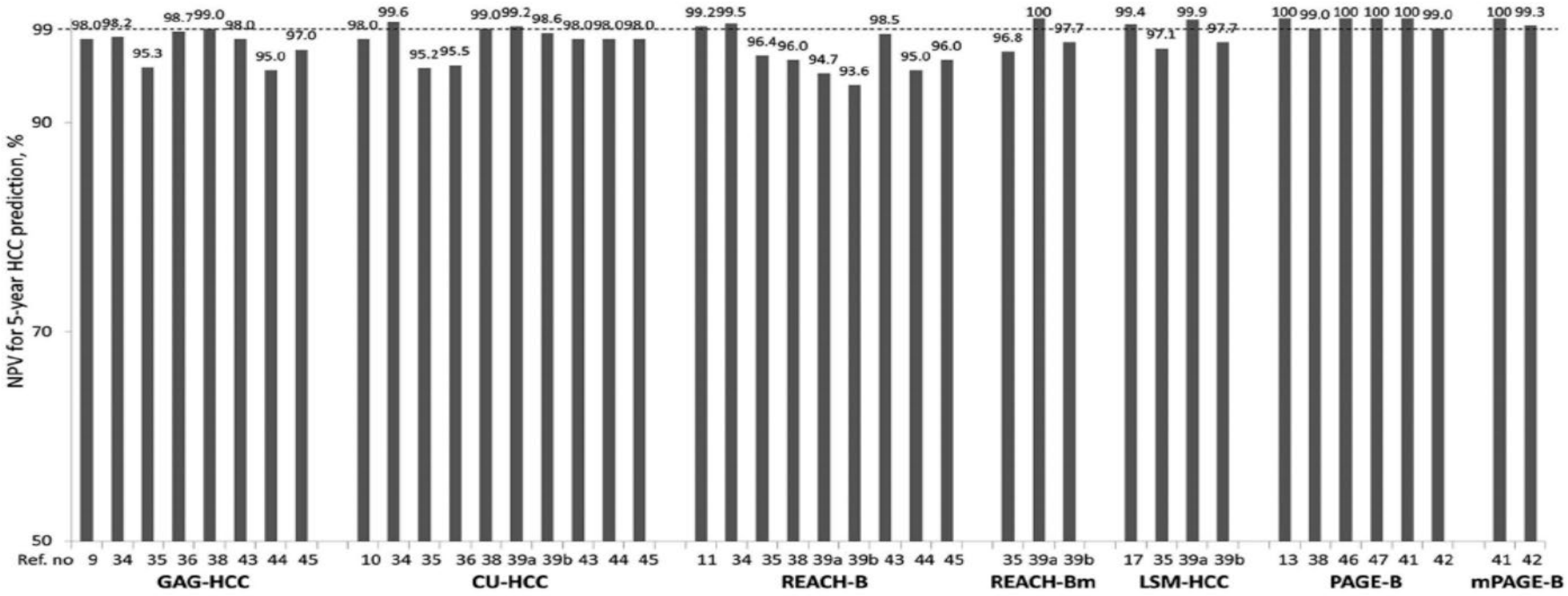
Should HCC Surveillance Be Relaxed in Treated Patients at Low Risk of HCC?

Should HCC Surveillance Be Enhanced in Patients at Higher Risk of HCC?

Can cirrhosis be safely excluded in all cases?

Should we mind of those co-morbidities that may promote liver disease progression?

Should HCC Surveillance Be Relaxed in Treated Patients at Low Risk of HCC?



NPV of the low-risk cut-off for 5-year prediction of HCC

Voulgaris T et al Liver Intern 2020

Summary

The risk of hepatocellular carcinoma decreases after long-termNAs treatment in Caucasians with chronic hepatitis B particularly in patients with Cirrhosis

PAGE-B represents a simple and reliable score for prediction of HCC risk in Caucasian CHB patients under NAs

Most patients who were low- or medium-risk at baseline by PAGE-B either remained at those risk categories or shifted to a lower risk group after 8 years of NAs therapy

Patients who were at low risk at baseline with PAGE-B score could HCC surveillance be relaxed

XVII INTERNATIONAL SYMPOSIUM

VIRAL HEPATITIS AND BEYOND

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Sitges
October 2025
3rd & 4th