



# European Young Hepatologists Workshop

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## *Can we predict HCC in chronic viral hepatitis?*

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# Can We Predict HCC in Chronic Viral Hepatitis

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## Outline

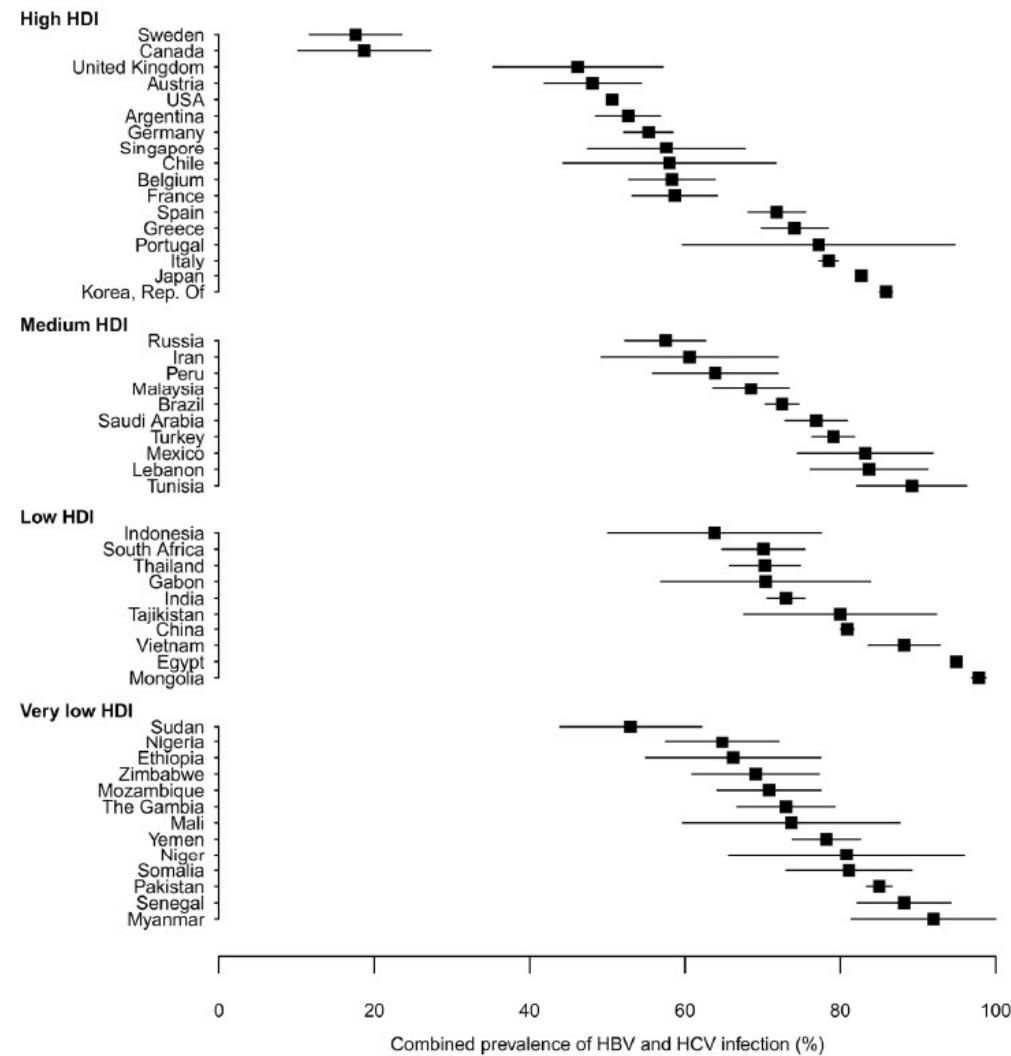
- Risk factors for HCC in HBV & HCV patients
- Risk scores for HCC in viremic patients
- Risk scores for HCC in non viremic patients
- Screening for HCC: in search of optimization

# Risk Factors for HCC. Estimates of the Attributable Fractions (%)

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Risk factors	Europe / US	Japan	Africa / Asia
<u>Hepatitis B virus</u>	22 (4-58)	20 (18-44)	60 (40-90)
<u>Hepatitis C virus</u>	60 (12-72)	63 (48-94)	20 (9-56)
Alcohol	45 (8-57)	20 (15-33)	- (11-41)
Tobacco	12 (0-14)	40 (9-51)	22 -
Af atoxin	Limited	Limited	High exposure
Other	< 5	-	< 5

# HCC Cases Positive for HBsAg or Anti-HCV or Both



# Factors Affecting HCC Risk in HBV Patients

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## Virus

Virus load  
Genotype (C)  
Pre-S mutations  
Enhancer-H mutations (T 1653)  
Core promoter mutations (V 1753,T 1762,A 1764)

## Host

Increasing age  
Male gender  
Cirrhosis  
Diabetes/Obesity  
Genetic polymorphisms (SNIPs)

## Environment

Af toxin  
Alcohol/Tobacco

# Factors Affecting HCC Risk in HBV Patients West vs East

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Factor	West	East
Age of acquisition	Older	Younger
Duration of infection	Shorter	Longer
Host genetics	?	Familial aggregation
HBV genotype	A, D	B, C
Environmental factors	Alcohol	Aflatoxin
Co-morbidities	Diabetes	Diabetes

# Factors Affecting HCC Risk in HCV Patients

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## Virus

Genotype

Core region mutations (e.g., 5' UTR)

## Host

Increasing age

Male

Advanced liver disease severity

Hepatocarcinogenesis/BMI

Diabetes

Genetic predisposition

## Environment

Alcohol

Tobacco

HBV

HIV

**Treatment failure!**

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# Risk scores for Hepatocellular Carcinoma in HBV Patients at Risk

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Risk score	Variables	Externally validated
Yang et al. (REACH-B)	Age, gender, ALT, HBeAg status, HBV DNA concentration	Yes (only in Asia)
Wong et al. (CU-HCC)	Age, albumin, bilirubin, HBV DNA concentration, cirrhosis	No
Yuen et al (GAG-HCC)	Age, gender, HBV DNA concentration, core promoter mutation, cirrhosis	No

# Risk Score for HCC in Chronic HBV. REACH-B

	3 years	5 years	10 years
0	0·0%	0·0%	0·0%
1	0·0%	0·0%	0·1%
2	0·0%	0·0%	0·1%
3	0·0%	0·1%	0·2%
4	0·0%	0·1%	0·3%
5	0·1%	0·2%	0·5%
6	0·1%	0·3%	0·7%
7	0·2%	0·5%	1·2%
8	0·3%	0·8%	2·0%

	3 years	5 years	10 years
9	0·5%	1·2%	3·2%
10	0·9%	2·0%	5·2%
11	1·4%	3·3%	8·4%
12	2·3%	5·3%	13·4%
13	3·7%	8·5%	21·0%
14	6·0%	13·6%	32·0%
15	9·6%	21·3%	46·8%
16	15·2%	32·4%	64·4%
17	23·6%	47·4%	81·6%

Age, gender, ALT, HBeAg, HBV-DNA

# Risk Score for HCC in Patients with HBV. CU-HCC

Measure	5-Year Prediction		10-Year Prediction	
	Value	95% CI	Value	95% CI
Cutoff score	5		5	
Area under ROC curve	0.76	0.66 to 0.86	0.78	0.71 to 0.86
Sensitivity, %	78.3	74.3 to 82.2	81.0	77.2 to 84.7
Specificity, %	72.8	68.5 to 77.2	75.7	72.0 to 79.3
Positive predictive value, %	14.2	10.9 to 17.5	26.8	22.6 to 31.0
Negative predictive value, %	98.3	89.6 to 100.0	97.3	89.3 to 100.0
Positive likelihood ratio	2.88	2.84 to 2.92	3.33	3.29 to 3.36
Negative likelihood ratio	0.30	0.26 to 0.34	0.25	0.21 to 0.29

Abbreviations: HCC, hepatocellular carcinoma; ROC, receiver operating characteristic.

**Age, albumin, bilirubin, HBV-DNA, cirrhosis**

# CU-HCC. Liver Stiffness-based Optimization of HCC Risk Score in Patients with HBV

## Components of LSM-HCC score

Factors	Score*
Age	
>50 yr	+10
≤50 yr	0
Albumin	
≤35 g/L	+1
>35 g/L	0
HBV DNA	
>200,000 IU/ml	+5
≤200,000 IU/ml	0
Liver stiffness	
≤8.0 kPa	0
8.1-12.0 kPa	+8
>12.0 kPa	+14

## 3-year prediction

	Value	95% CI
AUROC	0.89	0.84-0.95
Cutoff value	11	
Sensitivity (%)	100	67.6-100
Specificity (%)	70.7	66.6-74.5
PPV (%)	5.1	2.5-9.7
<u>NPV (%)</u>	<u>100</u>	<u>99.0-100</u>
LR+	3.4	3.0-3.9
LR-	∞	∞
No. at low risk	362 (69.6%)	
No. at high risk	158 (30.4%)	

# Risk Score for HCC in Patients with HBV. GAG-HCC

<i>Total study population</i>	5-year prediction	
	Value	95% CI
Optimal cut-off	100	
Sensitivity	67.8%	(62.4%, 99.3%)
Specificity	88.1%	(59.0%, 91.5%)
Positive predictive value	20.9%	(9.4%, 27.9%)
<u>Negative predictive value</u>	98.3%	(98.1%, 99.9%)
Positive likelihood ratio	5.72	(2.24, 8.37)
Negative likelihood ratio	0.37	(0.01, 0.43)

**Age, gender, HBV-DNA, core promoter mutation, cirrhosis**

# The Applicability of HCC Risk Prediction Scores in a North American Patient Population with HBV

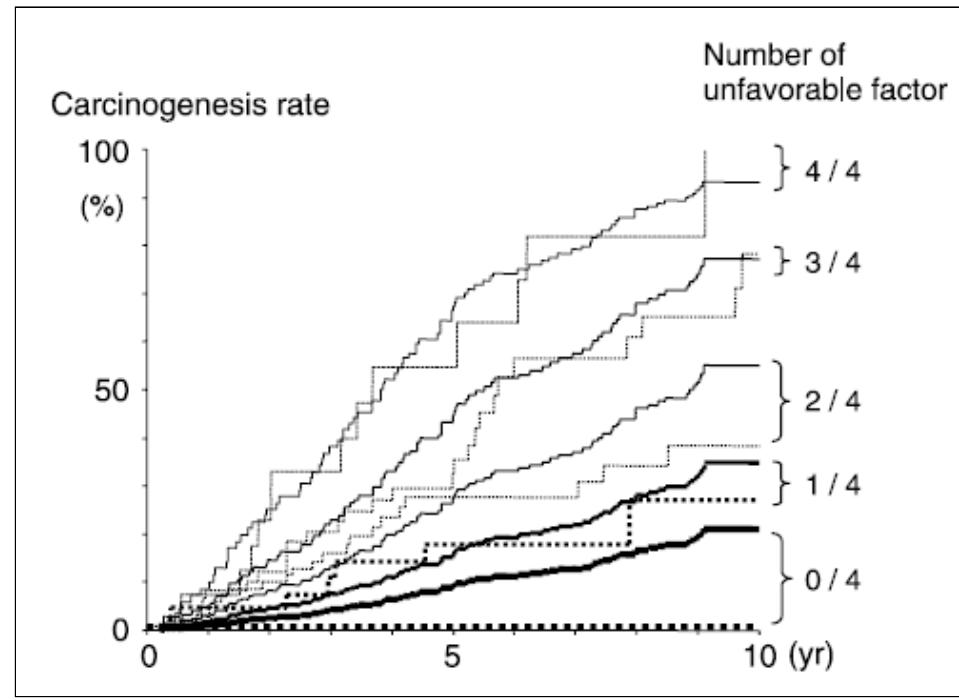
	5-year HCC risk	
	Predicted incidence	Observed incidence ( $\pm 95\% \text{ CI}$ )
<b>CU-HCC model</b>		
Low risk (n=1385)	0.9	0.49 (0.2 to 1.2)
Medium risk (n=300)	5.5	7.3 (4.4 to 12.0)
High risk (n=420)	21.2	8.5 (6.1 to 12.0)
<b>REACH-B model</b>		
Low risk (n=299)	0.067	0
Medium risk (n=1398)	1.4	2.4 (1.6 to 3.6)
High risk (n=408)	21.4	8.6 (6.0 to 12.3)
<b>NGM1-HCC model</b>		
Low risk (n=727)	0.17	0.2 (0.03 to 1.4)
Medium risk (n=1265)	3.3	4.0 (2.9 to 5.6)
High risk (n=113)	43.1	14.5 (8.2 to 24.7)
<b>NGM2-HCC model</b>		
Low risk (n=330)	0.07	0
Medium risk (n=1454)	2.6	2.5 (1.7 to 3.7)
High risk (n=321)	39.8	9.8 (6.7 to 14.3)
<b>GAG-HCC model*</b>		
Low risk (5-year n=1637, 10-year n=1338)	NA	1.1 (0.6 to 1.9)
High risk (5-year n=451, 10-year n=767)	NA	9.8 (7.2 to 13.3)

# Risk Scores for Hepatocellular Carcinoma in Patients with HCV

Risk score	Variables	Population	Externally validated
Ikeda et al	Age, gender, platelets, AFP	Cirrhosis	Yes
Lee et al (REVEAL)	Age, ALT, AST:ALT ratio, HCV-RNA, genotype, cirrhosis	HCV-RNA pos	Yes
Lok et al (HALT-C)	Age, race, platelets, alk phos, smoking, EV	Advanced HCV	No
EI Serag et al	Age, ALT, platelets, AFP	Chronic hepatitis	No
Gavilan et al (HCC4)	Age, $\gamma$ globulin, platelets, AFP	Chronic hepatitis	No

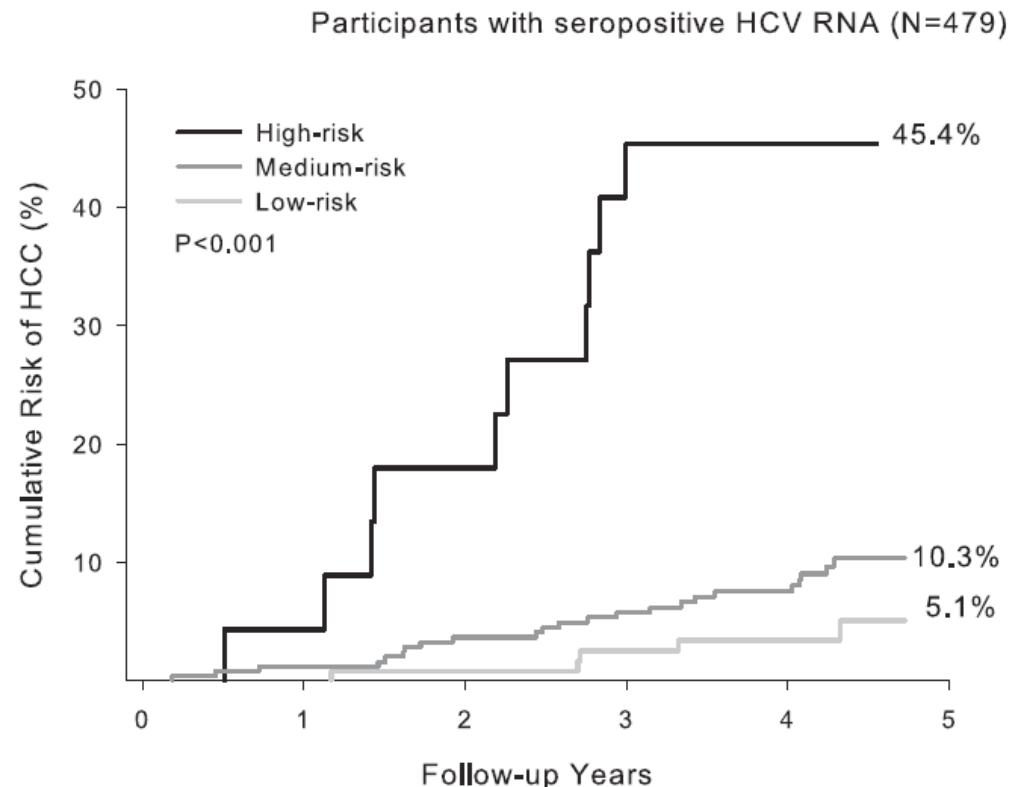
# Prediction Model of Hepatocarcinogenesis for Patients with HCV Cirrhosis

Factors	Category
Alpha-fetoprotein	0: < 20 (ng/ml) 1: $\geq 20$ (ng/ml)
Age	0: < 55 (year) 1: $\geq 55$ (year)
Sex	0: Female 1: Male
Platelet count	0: $\geq 100,000/\text{mm}^3$ 1: $< 100,000/\text{mm}^3$
Patient groups	0: Study cohort 1: Internal validation cohort 2: External validation cohort



# Predicting Risk of HCC in Asymptomatic Individuals Seropositive for Anti-HCV Antibodies

Sum of risk score	5-year predicted risk (95% CI), %
0	0.10 (0.03–0.14)
1	0.13 (0.04–0.19)
2	0.18 (0.05–0.26)
3	0.24 (0.07–0.36)
4	0.33 (0.09–0.49)
5	0.45 (0.13–0.66)
6	0.61 (0.17–0.90)
7	0.84 (0.23–1.23)
8	1.14 (0.32–1.67)
9	1.55 (0.43–2.26)
10	2.11 (0.59–3.07)
11	2.86 (0.80–4.17)
12	3.88 (1.09–5.63)
13	5.25 (1.48–7.60)
14	7.08 (2.02–10.21)
15	9.52 (2.74–13.65)
16	12.75 (3.71–18.13)
17	16.96 (5.02–23.87)
18	22.38 (6.78– 31.04)



# Can We Predict HCC in Chronic Viral Hepatitis

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- Risk factors for HCC in HBV & HCV patients
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# Recommendations for Surveillance in Patients Responding to Antiviral Therapy

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AASLD<sup>1</sup>

HBV      Surveillance should be continued in cirrhotics after HBsAg clearance or remission of inflammation

HCV      treatment related regression of cirrhosis is not a reason to withhold surveillance

EASL/EORTC<sup>2</sup>

Surveillance should be offered to treated patients with chronic hepatitis B and SVR patients with advanced HCV

# Prevention of Hepatitis B-related HCC by NUCs Propensity Score Studies

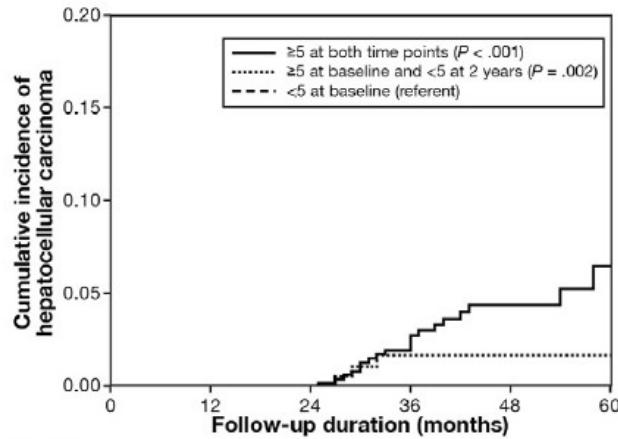
Author	Patients		Follow-up (yr)		HCC % at 5 yr		RR (95% C.I.)	P-value
	NUC+	NUC-	NUC+	NUC-	NUC+	NUC-		
Wu et al <sup>1</sup> (Taiwan)	21,595	21,595	3.4	5.2	7.3	22.7	0.31 (0.27–0.53)	<.001
Hosaka et al <sup>2</sup> (Japan)	316	316	3.3	7.6	3.7	13.7	0.37 (0.15–0.91)	.03
Kumada et al <sup>3</sup> (Japan)	117	117	12.3	11.6	2.7	11.3	0.28 (0.13–0.62)	.002
Gordon et al <sup>4</sup> (United States)	820	1,851	5.2	5.2	n.a.	n.a.	0.48 (0.27–0.86)	<.01

n.a. = not available

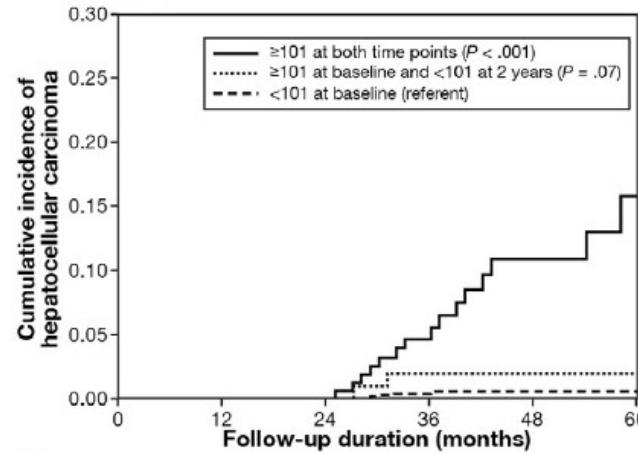
1. Wu CY, *Gastroenterology* 2014;147:143–151. 2. Hosaka T, *Hepatology* 2013;58:98–107. 3. Kumada T, *J Hepatol* 2013;58:427–433. 4. Gordon SC, *Clin Gastroenterol Hepatol* 2014;12:885–893.

# Risk Scores for HCC in Eastern HBV Patients Under Continuous Entecavir Treatment

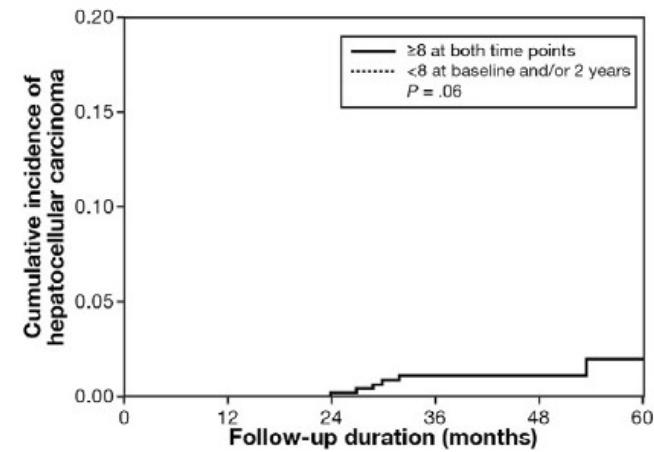
**CU-HCC**



**GAG-HCC**



**REACH-B**

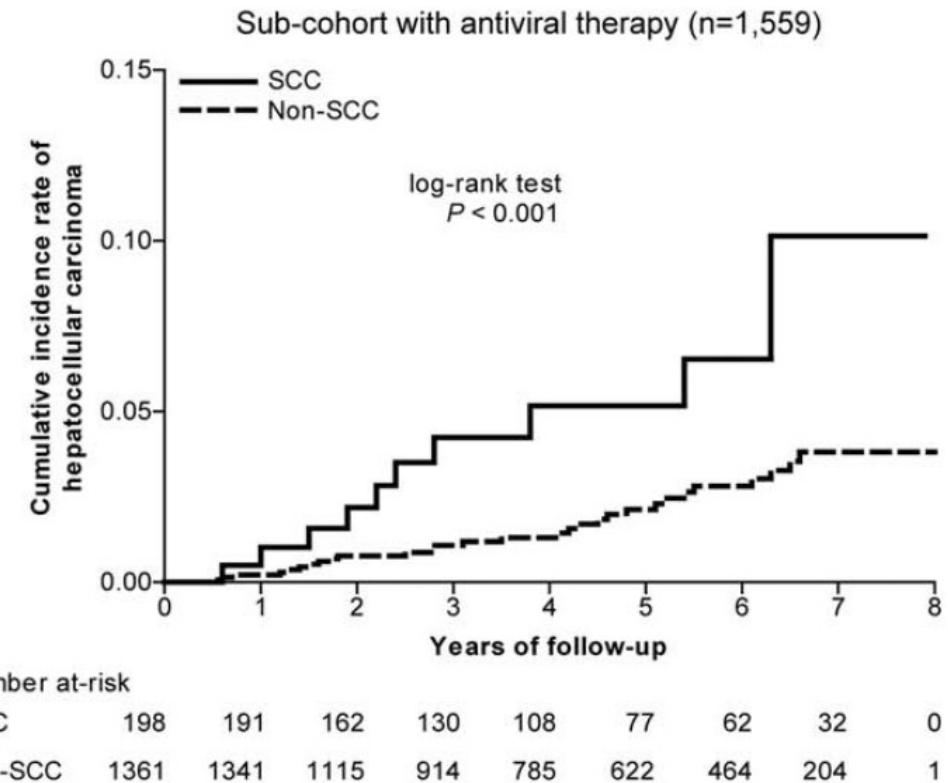
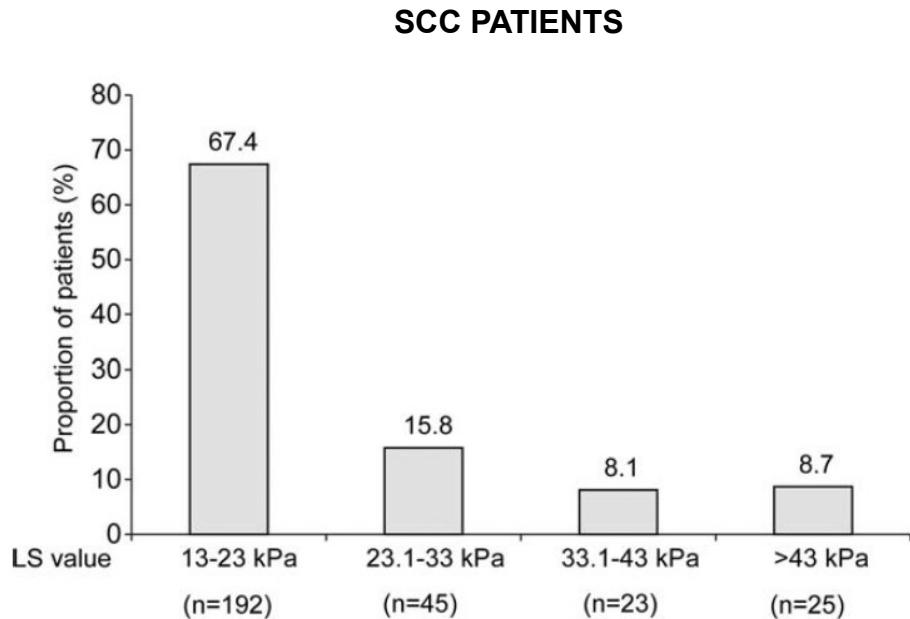


Age  
Albumin  
Bilirubin  
HBV-DNA  
Cirrhosis

Age  
Gender  
HBV-DNA  
Core promoter mutations  
Cirrhosis

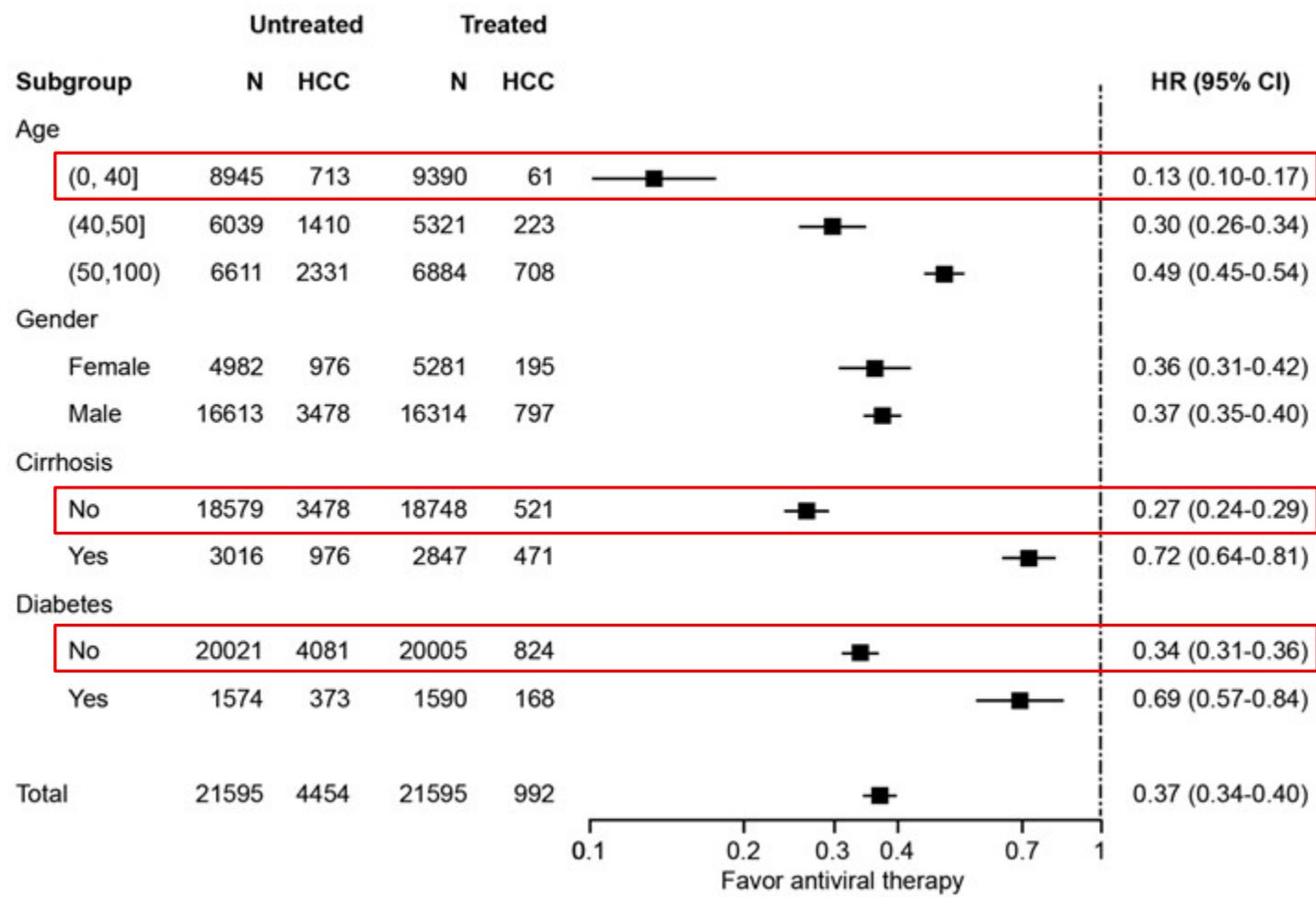
Age  
Gender  
ALT  
HBV-DNA  
HBeAg

# HCC Risk in Chronic Hepatitis B Patients with Transient Elastography–Defined Subclinical Cirrhosis



# HCC Risk in HBV Patients under NUC Therapy

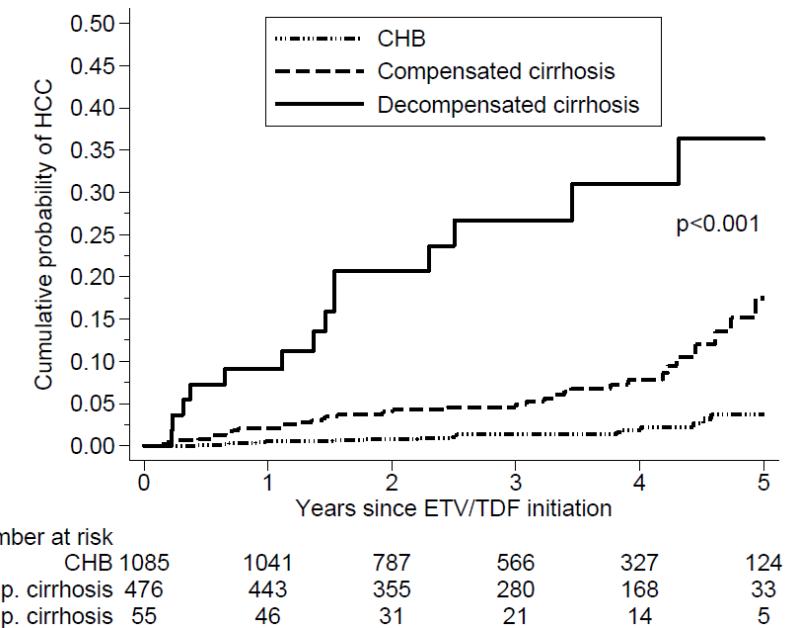
## A Nationwide Cohort Study, Taiwan



# Incidence of HCC in 1666 Western HBV Patients Treated with ETV/TDF by Liver Disease Severity

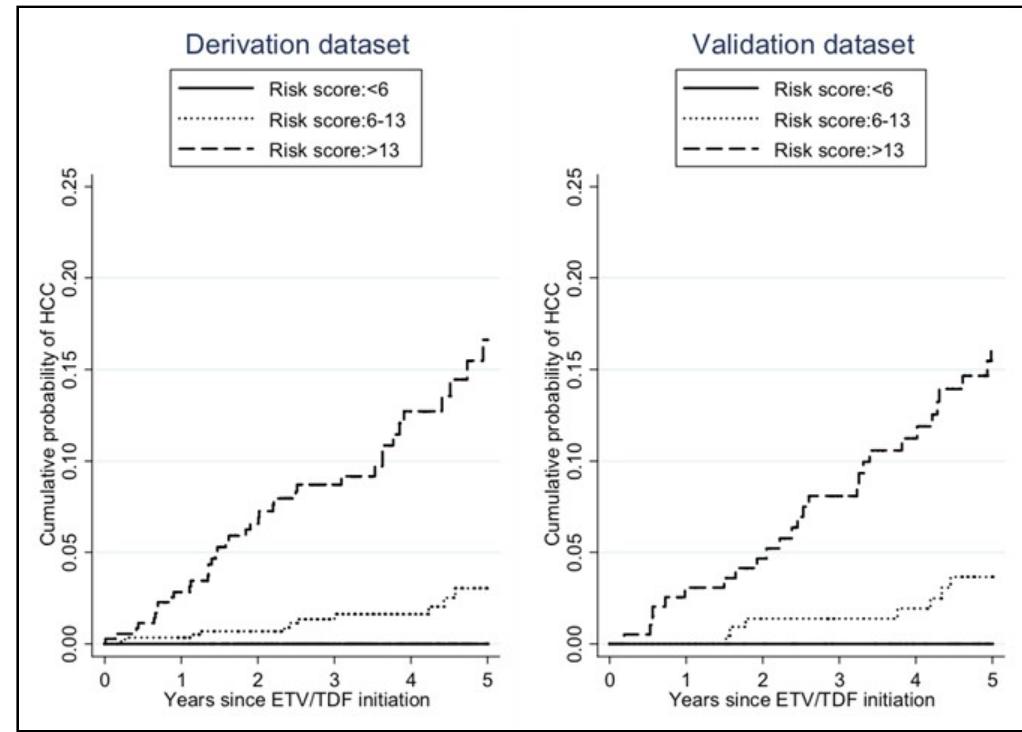
## Independent predictors of HCC    RR (95% C.I.)

<b>Age</b>	1.05 (1.03-1.08)
<b>Platelets</b>	0.99 (0.98-0.96)
<b>Compensated cirrhosis</b>	1.79 (0.94-3.38)
<b> Decompensated cirrhosis</b>	3.74 (1.44-8.23)



# PAGE-B Prediction Score for HCC in Caucasian HBV Patients under ETV or TDF

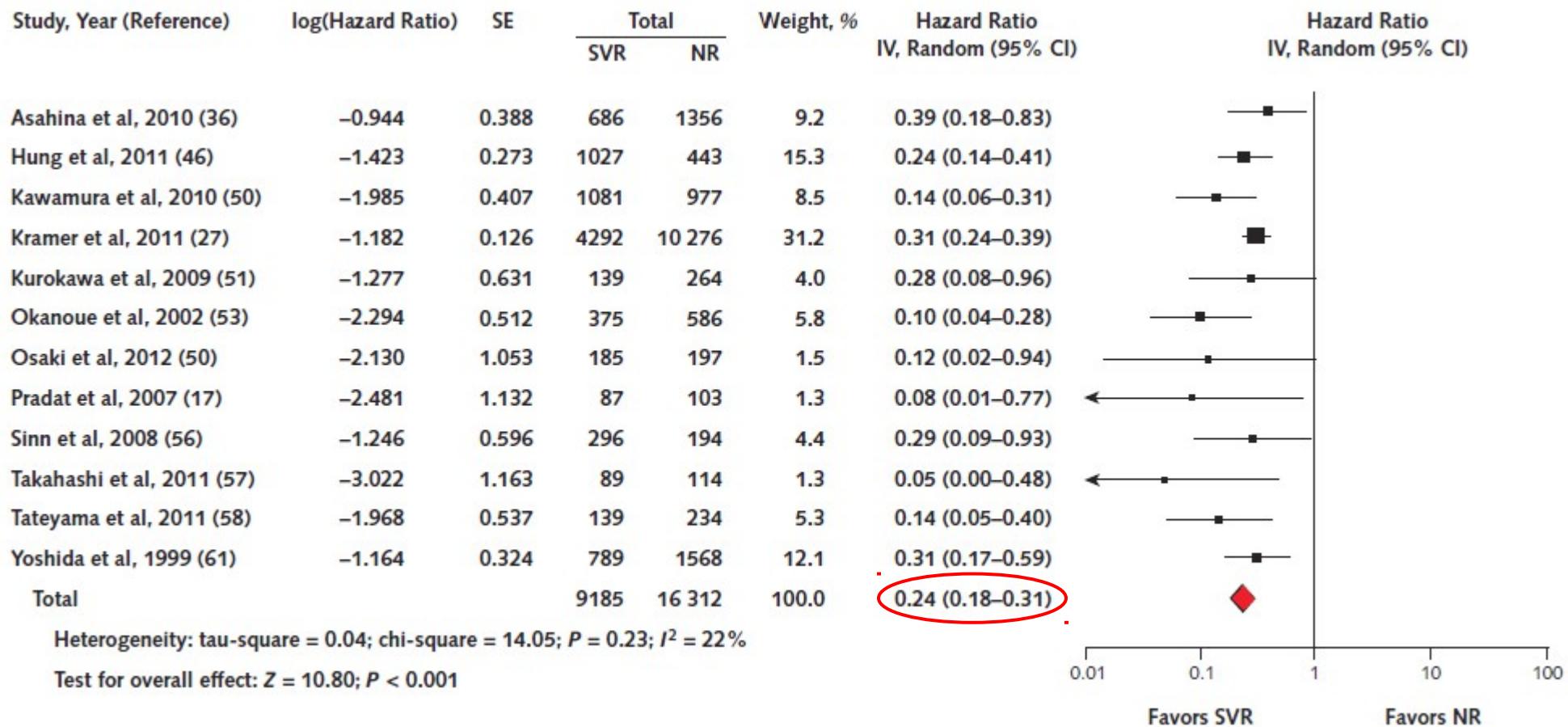
Age (years)	Gender	Platelets ( $\text{mm}^3$ )	
16-29: -4	Female: 0	$\geq 200,000$ :	0
30-39: -2	Male: 5	100,000-199,999:	6
40-49: 0		<100,000:	11
50-59: 2			
60-69: 4			
$\geq 70$ : 6			



# Eradication of HCV Infection and Development of HCC

## A Meta-analysis of Observational Studies

### Forest Plot Of Adjusted Hazard Effects In Persons At All Stages Of Fibrosis



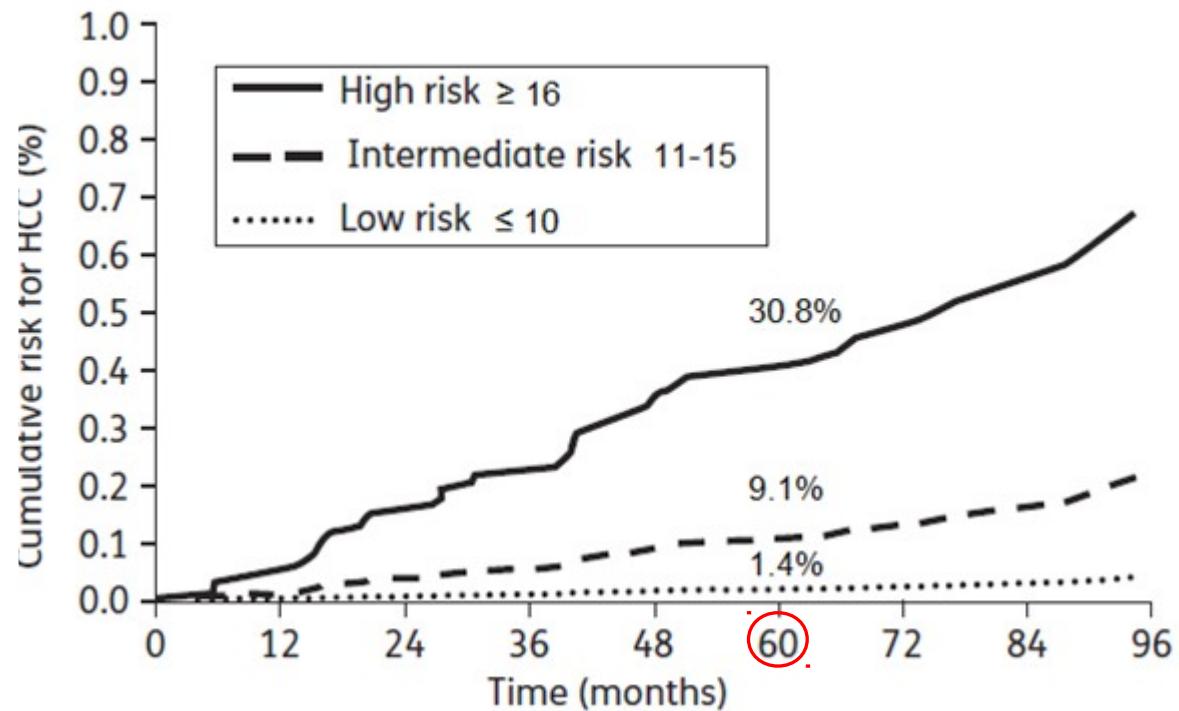
# Risk Score for HCC Development in Patients with HCV after SVR to PegIFN + RBV

## HCC Score

871 patients with SVR to PR

- Age  $\geq 60$  yr
- Platelets  $< 150 \times 10^9/L$
- AFP  $\geq 20$  mg/ml
- F3, F4

Auroc = 84.8%



# Risk Factors for HCC Development in HCV Patients Following IFN-based Therapy

Variable	CH + SVR	LC + SVR	CH + Non-SVR	LC + Non-SVR
No. of patients	1,751	149	2,118	284
Patients with T2DM	74	13	133	47
Patients with HCC	22	22	233	116
1,000 person years of HCC	1.55	18.23	13.53	50.43
TAI, kg, ≥200/<200*	<u>2.68</u> (1.14-6.34) <i>P= 0.024</i>	<u>3.84</u> (1.83-9.85) <i>P= 0.004</i>	<u>2.21</u> (1.65-2.95) <i>P&lt;0.001</i>	<u>1.54</u> (1.03-2.31) <i>P= 0.038</i>
T2DM, +/−*	<u>4.76</u> (1.60-14.10) <i>P= 0.005</i>	2.48 (0.57-10.86) <i>P= 0.228</i>	<u>2.53</u> (1.76-3.65) <i>P&lt;0.001</i>	<u>1.87</u> (1.16-3.01) <i>P= 0.010</i>

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- Risk factors for HCC in HBV & HCV patients
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# Surveillance for HCC as Recommended by AASLD, APASL and EASL

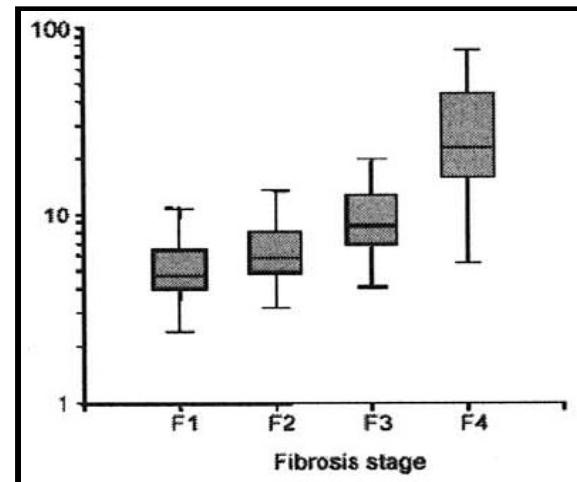
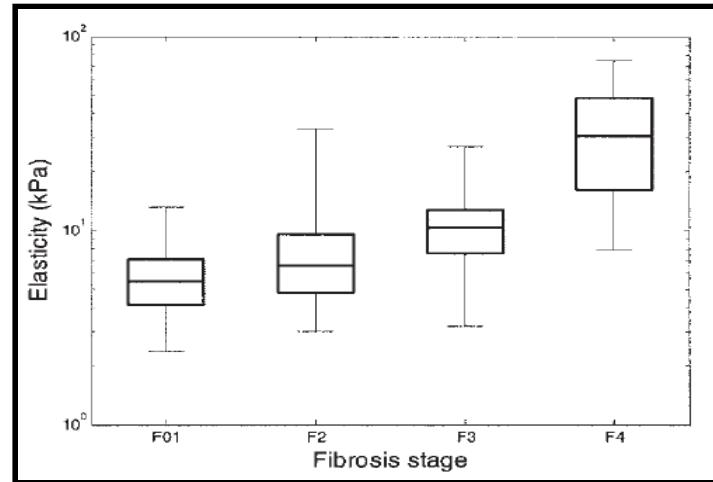
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STRATEGY	AASLD 2011	APASL 2010	EASL 2012*
Target population	Cirrhosis, CHB <sup>1</sup> NAFLD	Viral cirrhosis	Cirrhosis, CHB <sup>2</sup> HCV F3
	<b>1 Asian males &gt; 40 years and females &gt; 50 years Family history of HCC African/North American blacks &gt; 20 years</b>		<b>2 Active hepatitis Family history of HCC</b>

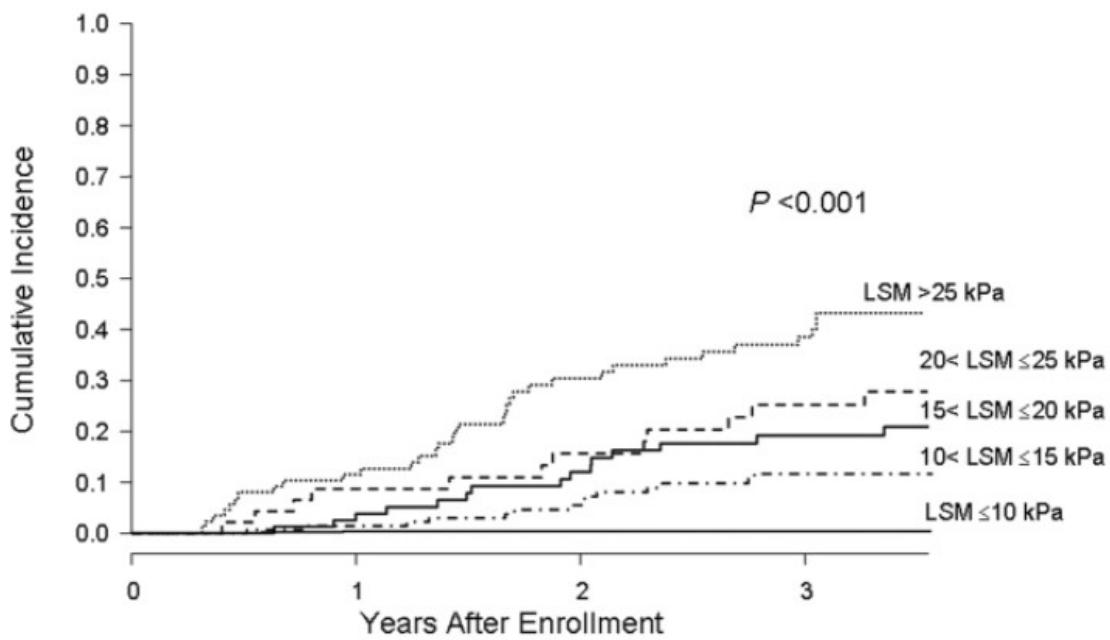
\*EASL-EORTC: Evidence 1B/3A recommendation 1A/B

# Prevalence of Fibrosis Stage and Diagnostic Accuracy of TE

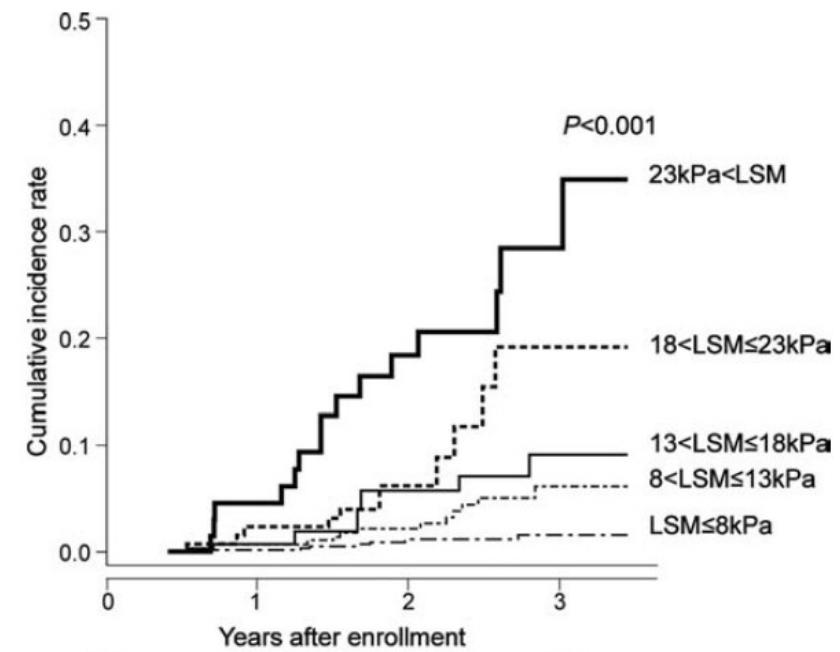
Disease	Fibrosis stage	Prev. (95%CI)	Sens. (95% CI)	Spec. (95% CI)
Hepatitis B	$F \geq 2$	0.53 (0.11-0.94)	0.77 (0.68-0.84)	0.72 (0.55-0.85)
	$F \geq 3$	0.39 (0.18-0.59)	0.83 (0.75-0.88)	0.81 (0.75-0.86)
	$F=4$	0.25 (0.001-0.57)	0.67 (0.57-0.75)	0.87 (0.83-0.91)
Hepatitis C	$F \geq 2$	0.54 (0.13-0.96)	0.76 (0.61-0.86)	0.86 (0.77-0.92)
	$F \geq 3$	0.33 (0.07-0.59)	0.88 (0.84-0.92)	0.91 (0.83-0.96)
	$F=4$	0.20 (0.001-0.47)	0.85 (0.77-0.91)	0.91 (0.87-0.93)



# Can HCC Be Predicted by Transient Elastography?



N = 866 HCV patients



N = 1130 HBV patients

# Complications and Competing Risks of Death in Compensated Viral Cirrhosis

	HCV-related cirrhosis (n=1308, 79.0%)	HBV-related cirrhosis (n=315, 19.1%)	HCV and HBV related cirrhosis (n=31, 1.9%)	Whole cohort (n=1654)
<b>Death</b>	<b>93 (7.1%)</b>	<b>6 (1.9%)</b>	<b>3 (10%)</b>	<b>102 (6.2%)</b>
<i>HCC-related</i>	17 (19.5%)	1 (16.6%)	0	18 (18.7%)
<i>Non-HCC liver-related</i>	27 (30.7%)	2 (33.3%)	1 (50%)	30 (31.2%)
<i>Bacterial infection</i>	13 (14.7%)	0	0	13 (13.5%)
<i>Extrahepatic cancer</i>	7 (7.9%)	3 (50%)	0	10 (10.4%)
<i>Cardiovascular disease</i>	5 (5.7%)	0	0	5 (5.2%)
<i>Other extrahepatic disease</i>	19 (21.5%)	0	1 (50%)	20 (20.8%)
<i>Missing data</i>	5	0	1	6

# Risk Score-guided Mass Ultrasonography Screening for HCC in Taiwan

Group (45-69 yr)	Age, ALT, AST, AFP Platelets, DMT2	# Patients	Total Screened	HCC #	x10 <sup>5</sup>
HBsAg/antiHCV (+)	Yes	3,754 (9.1%)	2,989 (77%)	15	5.0
	No	3,674 (8.9%)	2,730 (79%)	0	0
HBsAg/antiHCV (-)	Yes	8,975 (21.8%)	3,243 (10%)	1	0.3
	No	24,816 (60.2%)			
Total		41,219 (100,0%)			

Mortality Ratio (age & sex adjusted) = 0.69 (0.56-0.84) vs uninvited