MÁSTER EN HEPATOLOGÍA

UAM Universidad Autónoma de Madrid

Universidad de Alcalá

Asignatura: Cirrosis I

“Elastografía de transición en el diagnóstico y pronóstico de la enfermedad hepática crónica. Recomendaciones actualizadas de Baveno 7 ”

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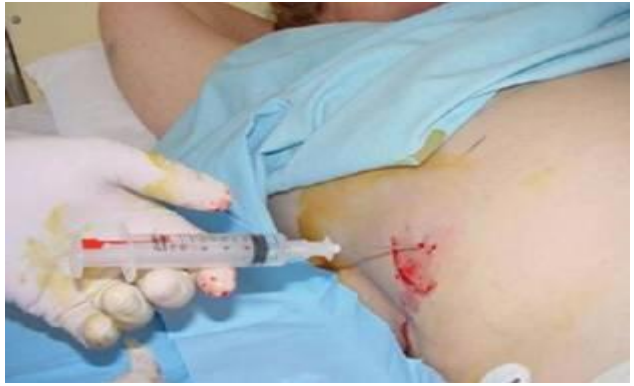
18-11-2021



› News › Technology & Science

Cutting wedge technology: Liver disease can be spotted by CHEESE scanner

23:59, 26 NOV 2013 | BY ANDREW GREGORY

Originally developed for farmers to test the ripeness of their product, medics have now found it can detect the life-threatening condition

39 SHARES

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Say cheese: Life-saving technology

When? Screening cirrhosis/P Hypertension

Before

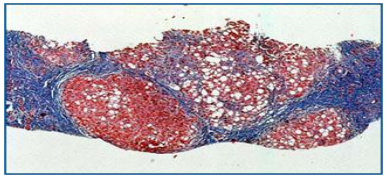
- **Clinically suspected or evident**
- **Signs, Labs, Imaging**
- **Liver biopsy**
- **Decompensation**

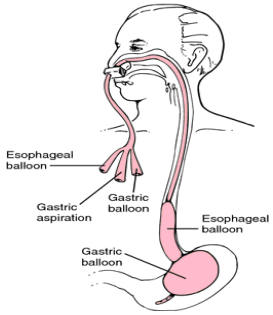
Now

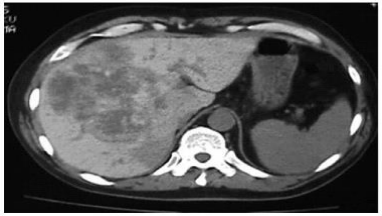
- **Always**
- **Non-invasive tests**

Pre-elastography era: unsuspected cirrhosis

- **Diabetes**
- **ALT 35**
- **GGT 60**
- **US steatosis**
- **Diet, weight**



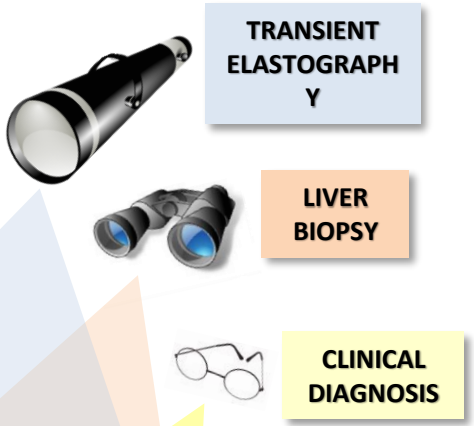




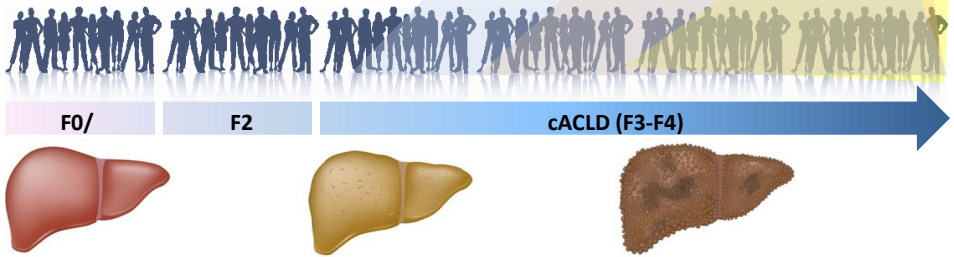
Impact of elastography in CLD

- Liver (spleen) stiffness by elastography (TE)
- CLD staging
- Essential to non-invasive assessment of CLD

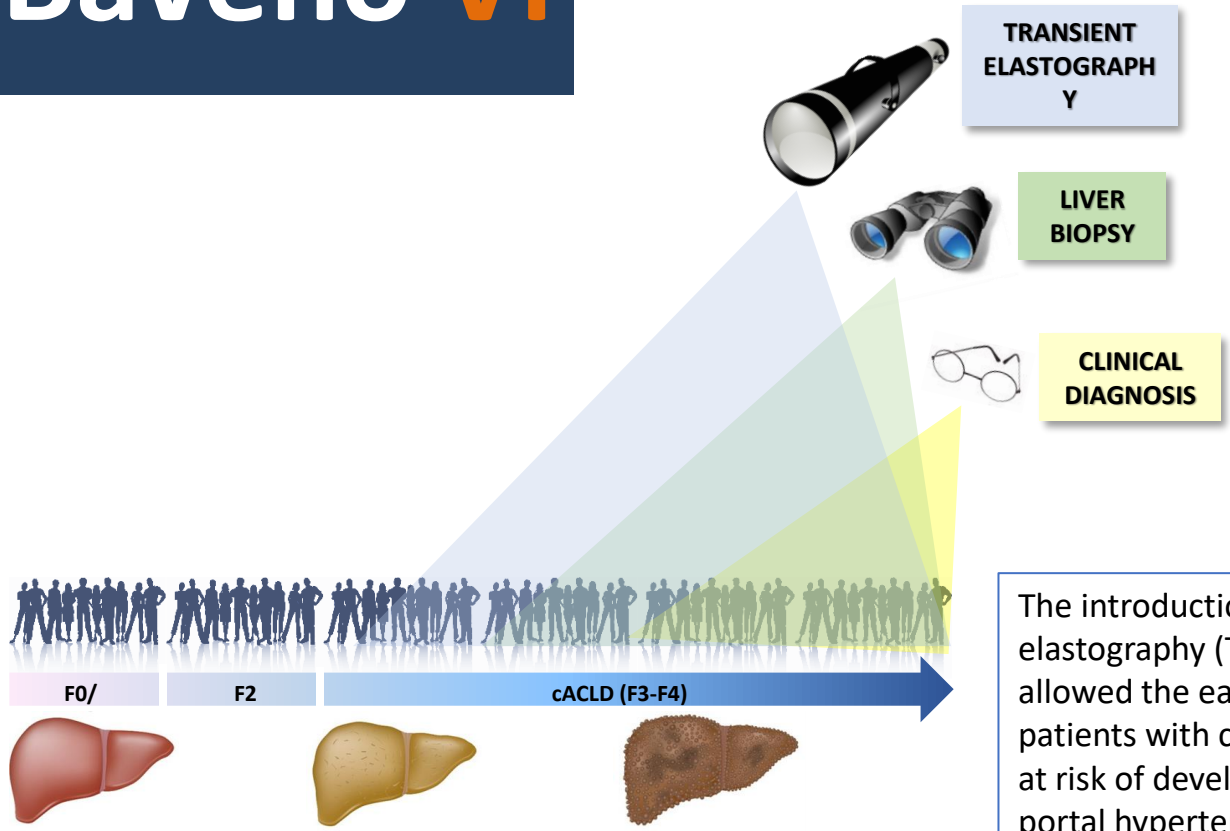
Applicability
Easiness
Repeatable
Rapidness



CHRONIC LIVER DISEASE



Baveno VI



The introduction of transient elastography (TE) in clinical practice has allowed the early identification of patients with chronic liver disease (CLD) at risk of developing clinically significant portal hypertension (CSPH) (1b; A).

Baveno VI

Compensated Advanced Chronic Liver Disease (cACLD)

LIVER STIFFNESS

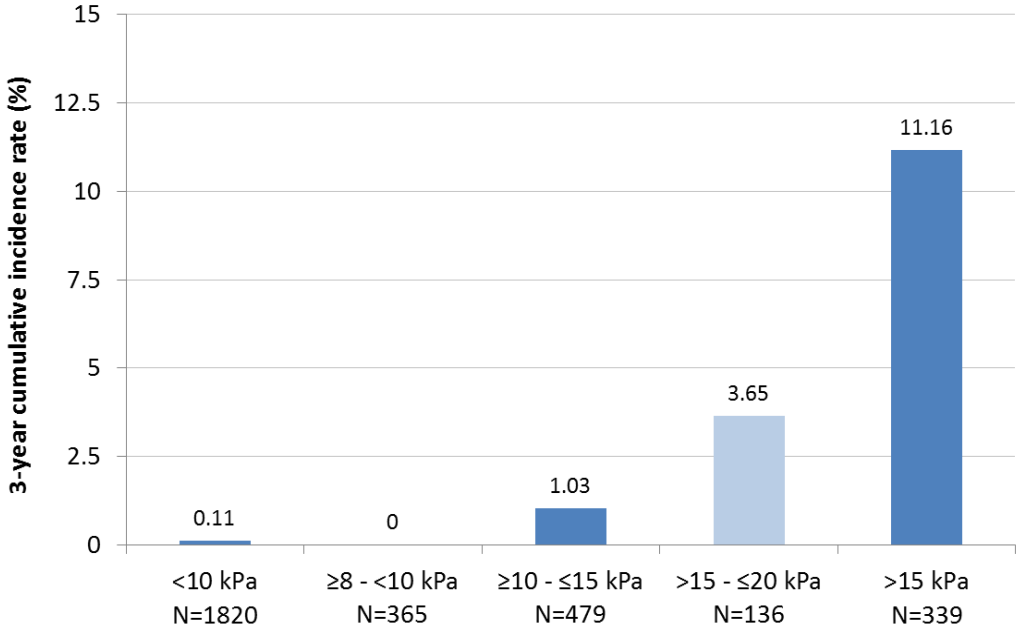
< 10 kPa | **> 15 kPa** | **< 10 kPa** | **> 15 kPa**

FIBROSIS STAGE (F3-F4) → **RISK OF LRE (DECOMP/L. DEATH)**

Study	Etiology	Patients (n)	Liver event	Follow-up (months)	LSM cut-off	Event rate
Masuzaki et al. 2009 [10]	HCV	866	HCC	36 (mean)	≤10 kPa	CI: 0.4% (3 years) ER: 2/511 (0.4%)
Fung, et al. 2011 [11]	HBV	528	LRD + HCC	35 (median)	<10 kPa	CI: 0 (3 years) ER: 0/445
Vergniol, et al. 2011 [13]	HCV	1457	OS	47.3 (median)	≤ 9.5 kPa	OS: 96% (5 years)
Jung&Kim, et al. 2011 [14]	HBV	1130	HCC	30.7 (median)	≤8 kPa	CI: 1.58% (3 years)
Coperchot, et al. 2012 [15]	PBC	150	LRE	28 (mean)	≤9.6 kPa	ER: 1/113 (0.8%)
Klibansky, et al. 2012 [16]	Mixed	400	LRE	28 (median)	<10.5 kPa	ER: 3/224 (1.3%)
Pang et al. 2014 [17]	Mixed	2052	LRE	15.6 (median)	<10 kPa	CI: 3.9% (3 years)
Coperchot, et al. 2014 [18]	PSC	168	LRE	48 (mean)	≤9.9 kPa	ER: 6/112 (5%) OS: 97% (3 years)
Tatsumi, et al. 2015 [19]	HCV	470	HCC	23 (median)	≤12 kPa	CI: 0 (2 years) ER: 1/363 (0.3%)
Shili-Masmoudi, et al. 2020 [20]	NAFLD	2245	LRE	27 (median)	≤12 kPa	CI: 0.2% (3 years) OS: 96.5% (3 years)
Rasmussen, et al. 2021 [20]	ALD	443	LRE*	49 (median)	<10 kPa	CI: 1.1% (3 years) ER: 9/303 (3%)
Grgurevic, et al. 2021 [21]	T2D	454	LRE	25 (median)	<9.6 kPa	ER: 0

CI: cumulative incidence
ER: event rate
LRD: liver-related mortality
OS: overall survival
LRE: liver-related events
*Including alcoholic hepatitis

Liver-related events during follow-up in different studies evaluating patients with chronic liver disease selected by a liver stiffness value below 10 kPa or similar values



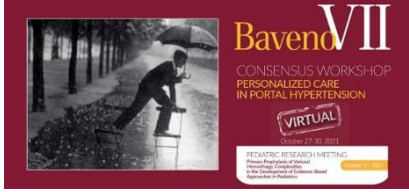
Liver-related events (3-year cumulative incidence rate) in a cohort of 2638 patients (France, Hong Kong, Canada, and Spain) with NAFLD distributed in subgroups defined by different liver stiffness cut-offs, including the values that define compensated advanced chronic liver disease (cACLD).

Baveno VII
CONSENSUS WORKSHOP
PERSONALIZED CARE IN PORTAL HYPERTENSION
October 27-30, 2021

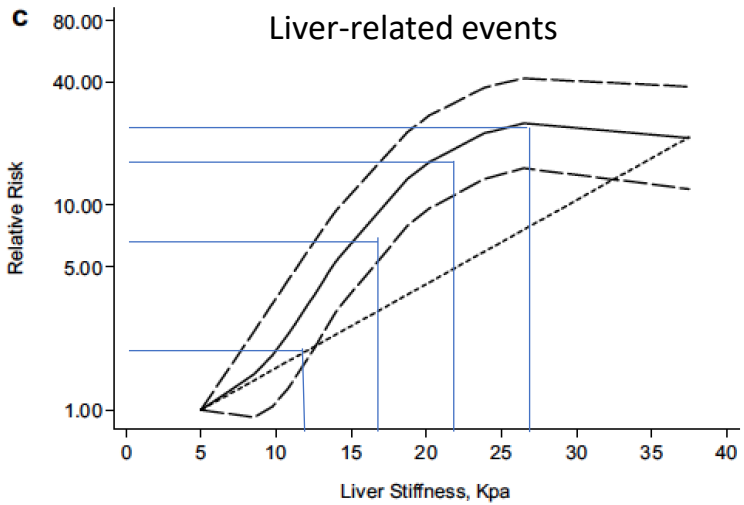
Outcome and Prognosis (All New)

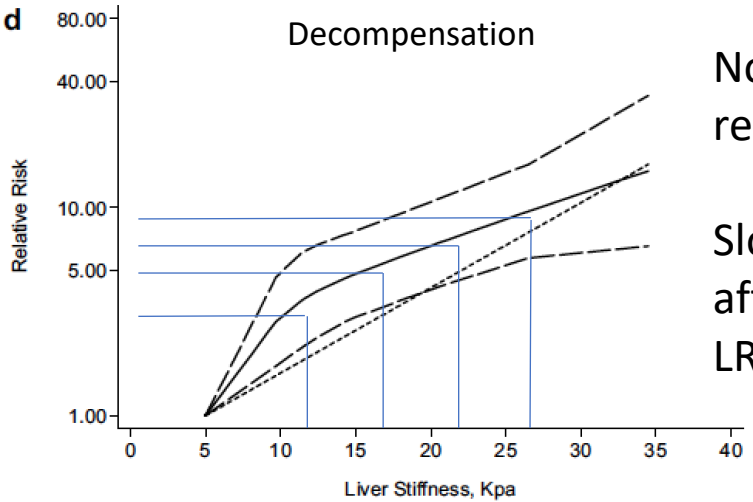
-LSM (irrespective of the technique used for its measurement) holds prognostic information in cACLD, both at index investigation and during follow-up (A;1).

-A rule of five for LSM by TE (10-15-20-25 kPa) should be used to denote progressively higher relative risks of decompensation and liver-related death independently of the etiology of CLD (B;1).



Dose-response between LSM and LRE or decompensation



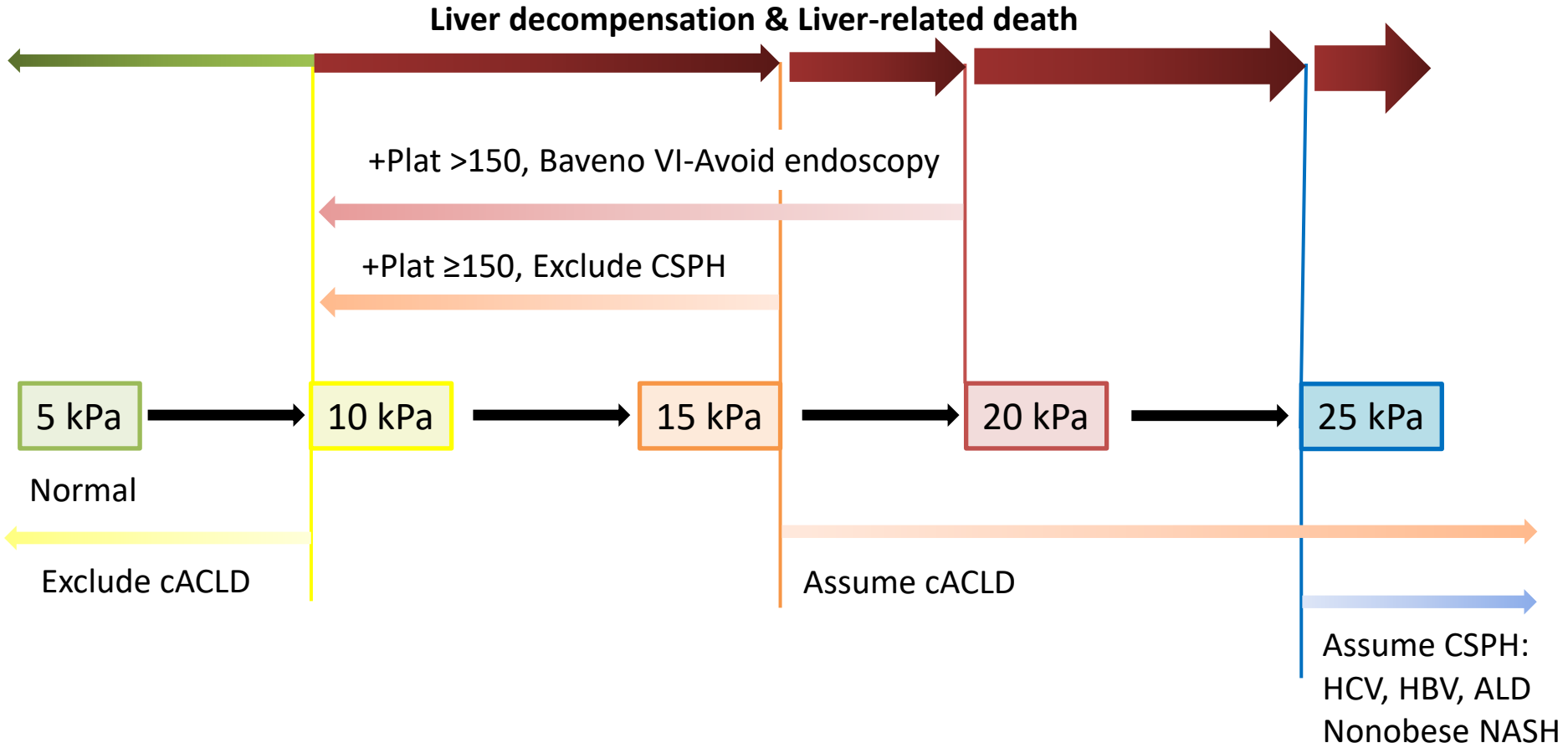


N>3,000 for LRE
N>6,000 for decompensation

Non-linear dose-response.

Slope flattens after 25 kPa for LRE.

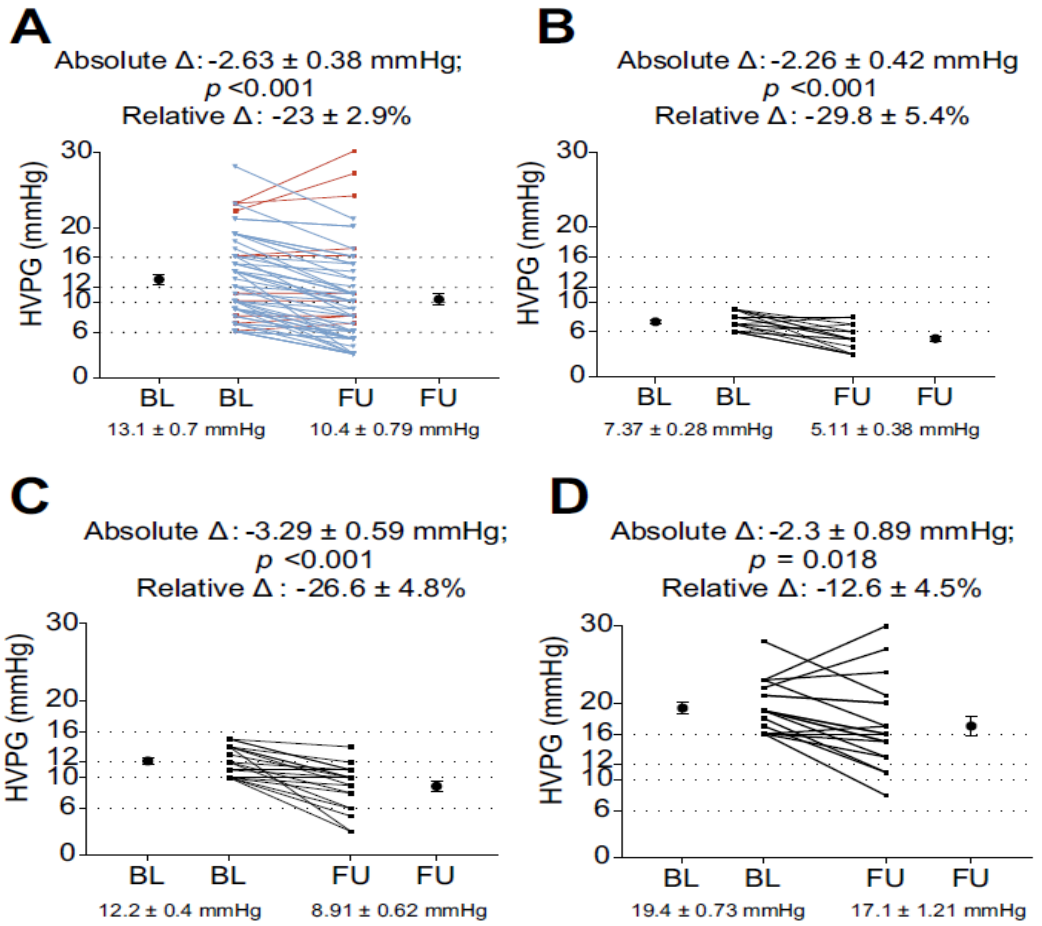
Shen, Hepatology Int 2019



Non-invasive prediction in cACLD by TE-summary: THE RULE OF FIVE

Fibrosis and LSM after SVR-DAA

-60 cirrhotic HCV patients
-SVR with DAA
-HVPG pre and post

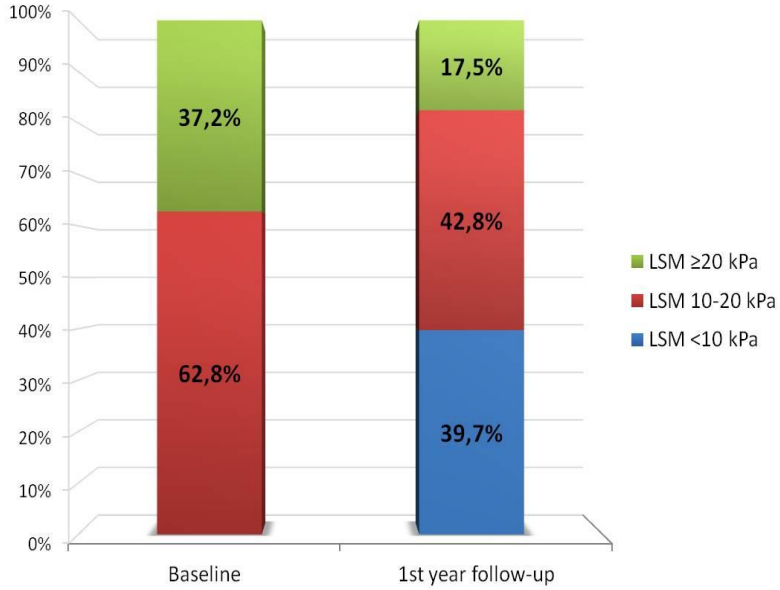


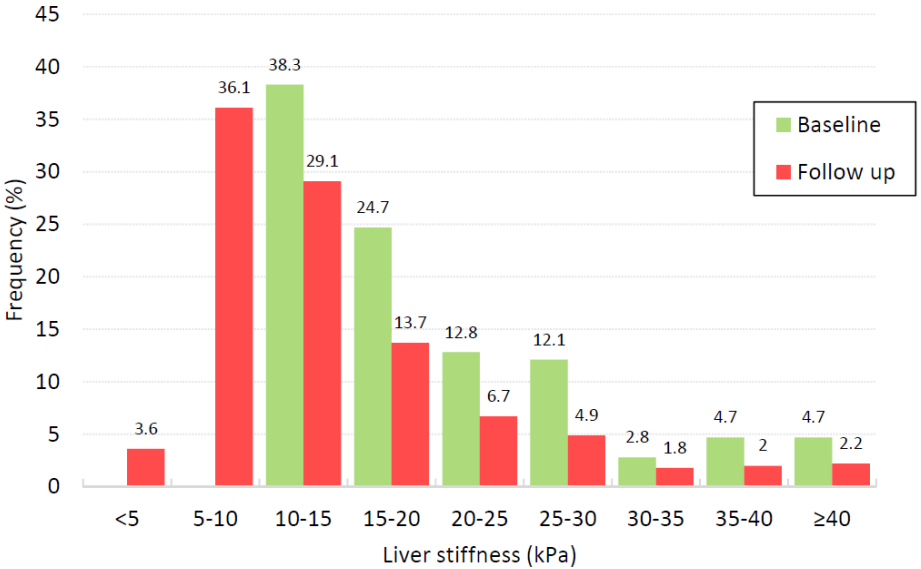
Basal HVPG <10 mmHg

Basal HVPG 10-15 mmHg

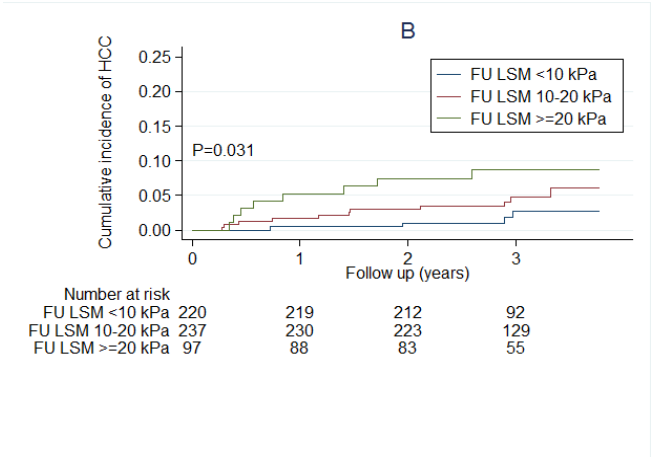
Basal HVPG ≥16 mmHg

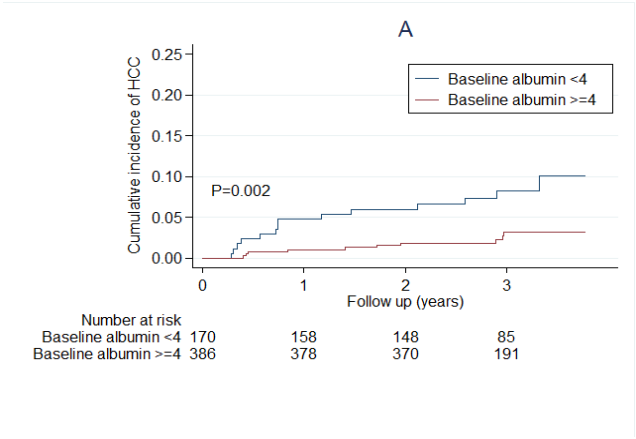
Mandorfer, et al. J Hepatol 2016

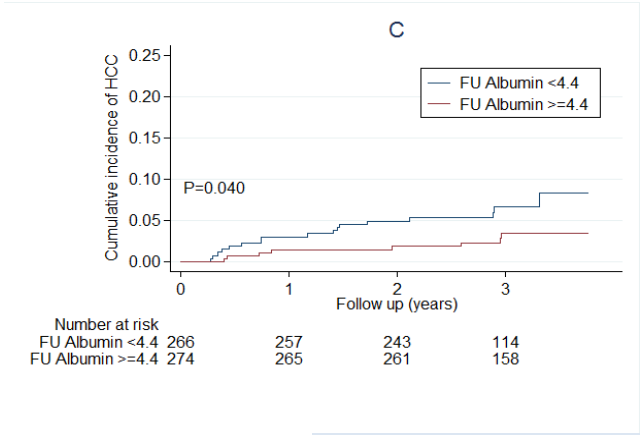




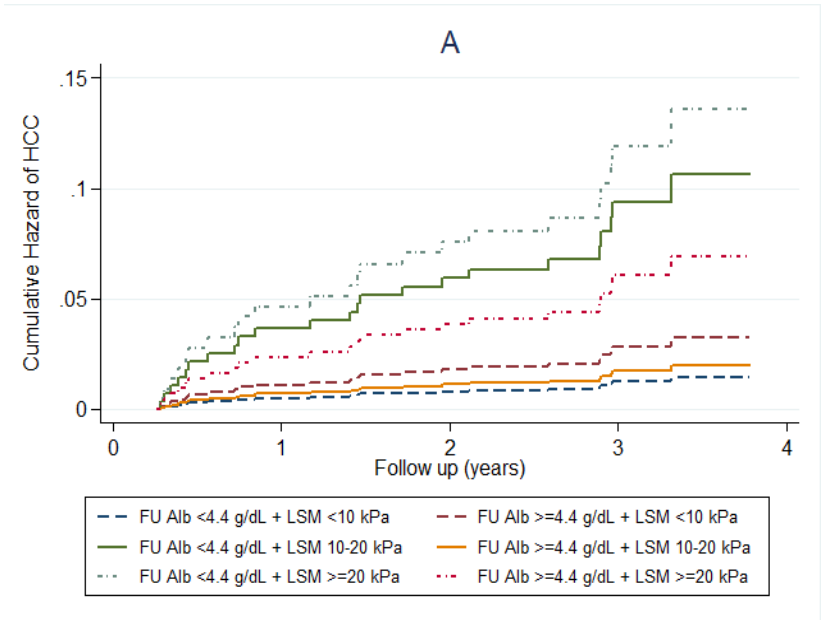
Pons, et al. J Hepatol 2020

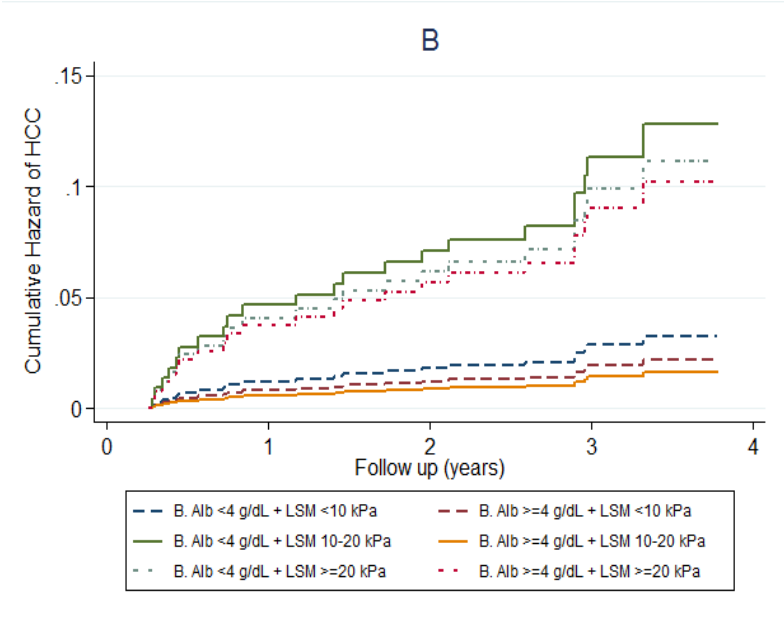




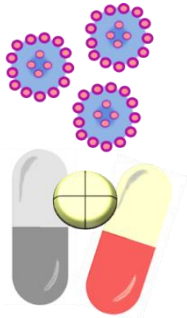


Pons, et al. J Hepatol 2020





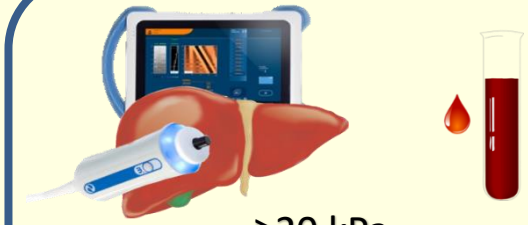
Pons, et al. J Hepatol 2020



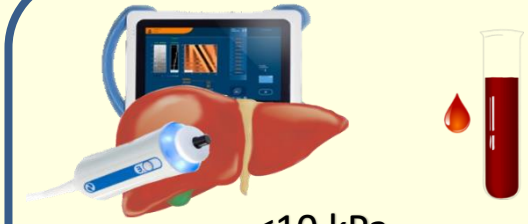
HCV
oral antiviral
therapy

SVR

Follow-up non-invasive tests

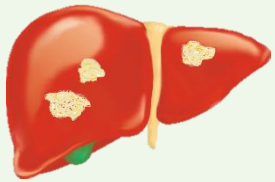


≥20 kPa
or
10-20 kPa + Albumin <4.4 g/dL

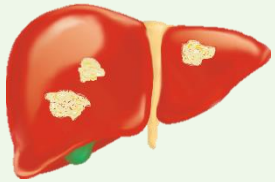


<10 kPa
or
10-20 kPa + Albumin ≥4.4 g/dL

HCC incidence rates



≥1.9/100 patient-years



<1/100 patient-years

Pons, et al. J Hepatol 2020

Baveno VII
CONSENSUS WORKSHOP
PERSONALIZED CARE IN PORTAL HYPERTENSION
October 27-30, 2021

Updated Recommendations

Panel 3/session 2, part 2

“Impact of aetiological therapies in the course of cirrhosis”

Suggested new title: “Portal hypertension management after removal/suppression of the primary etiological factor”

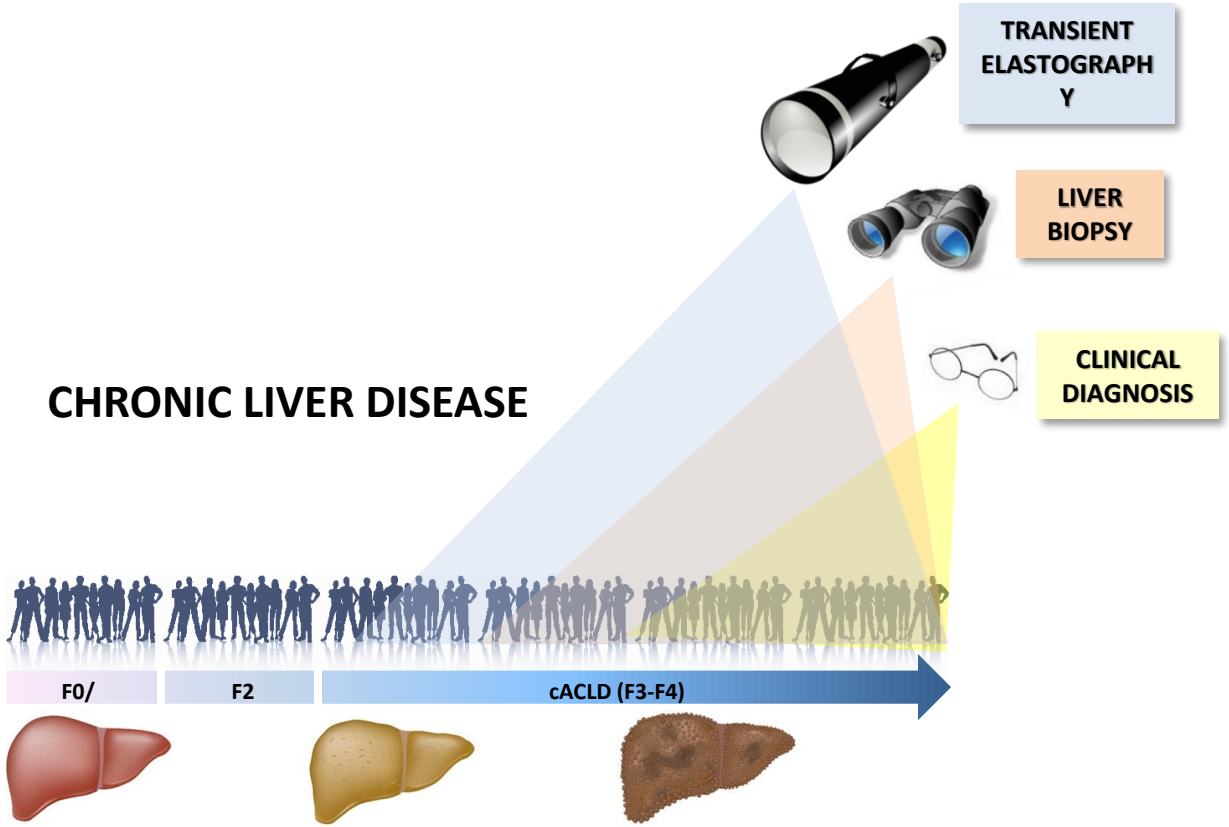
Panel 3/session 2, part 2 – "Impact of aetiological therapies in the course of cirrhosis"

- **B7: "Patients with HCV-induced cACLD who achieve SVR and show post-treatment improvements to liver stiffness measurement (LSM) values of <12kPa and PLT >150,000 can be discharged from portal hypertension surveillance, as they do not have CSPH. In the identified low-risk patients, HCC surveillance is the main concern."**

- Comment: New statement based on the individual patient data meta-analysis (uploaded; REF 1) the sensitivity of these criteria for CSPH is 99%; the reason for using such stringent criteria is that otherwise, in a very selected dataset (based on REF 2) of patients with pre-treatment CSPH who did not resolve CSPH 24 weeks after end of treatment and in whom HVPG was repeated at week 96 (i.e., a highly selected patient population), a relevant proportion of patients with CSPH would have been missed – for "discharging" patients, we want to be on the safe side. The risk of decompensation for patients meeting these criteria is 0% (based on REF 3), if considering HCC as a competing risk. These criteria are met 37.9% of unselected cACLD patients achieving SVR (based on an unpublished cohort of n=1972 patients). Thus, a relevant proportion of patients can be discharged from portal hypertension surveillance.

1. Uploaded document "SEMMLERLENSGARCIA-PAGANMANDORFER - INDIVIDUAL PATIENT DATA META-ANALYSIS SVR HVPG NIT - 211005.docx"
2. Lens and Baiges et al. Hepatology 2020
3. Semmler et al. Hepatology 2021

Impact of elastography in cACLD-varices



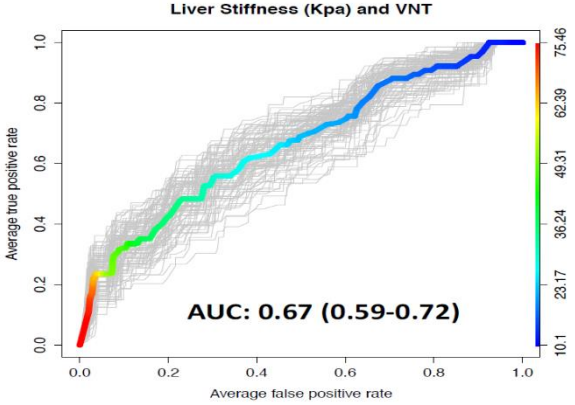
¿ENDOSCOPY EVERY cACLD PATIENT?

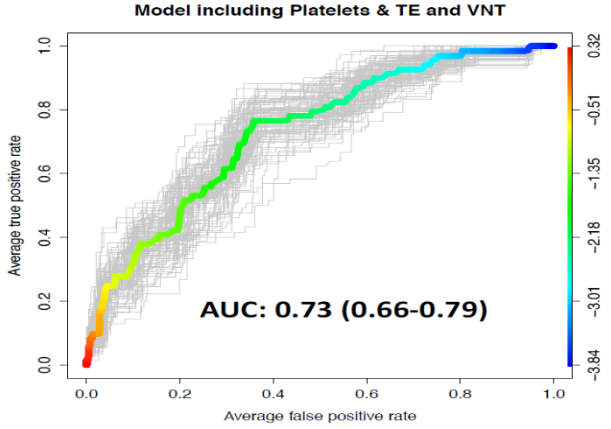
NO

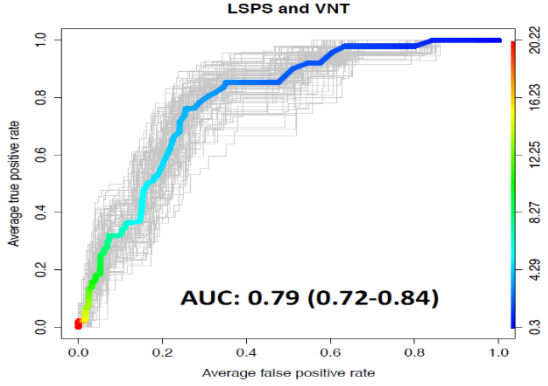
Ruling out varices in cACLD

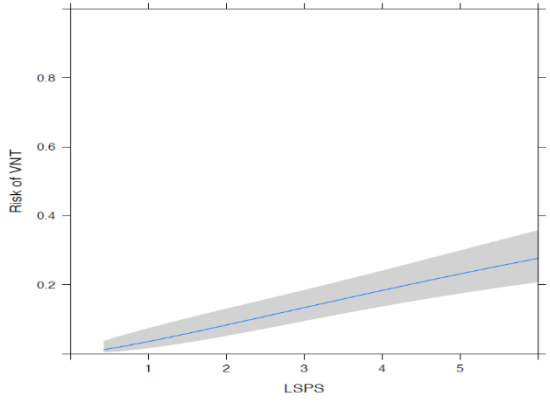
	No.	All varices	VNT	Classification rule	All varices NPV	VNT NPV	Varices missed	VNT missed	EGD avoided
Augustin, et al. 2014	49	20%	0	LSM<25 LSM<25+Pla≥150	93% 100%	100% 100%	4% 0	0 0	61% 20%
Montes, et al. 2012	85	45%*	20%	LSM<20 LSM<20 and/or Pla>120	90% 100%	- 100%	2.3% 0	- 0	25% 15%
Ding, et al. 2015	272	33%	10%	LSM<25+Pla≥100	-	100%	-	0	39%
ANTICIPATE 2015	379	42%	15%	LSM<25+Pla≥100 LSM<25+Pla≥150	79% 86%	95% 96.5%	9.5% 3%	2% 0.8%	45% 23%

Elastography: varices-cACLD



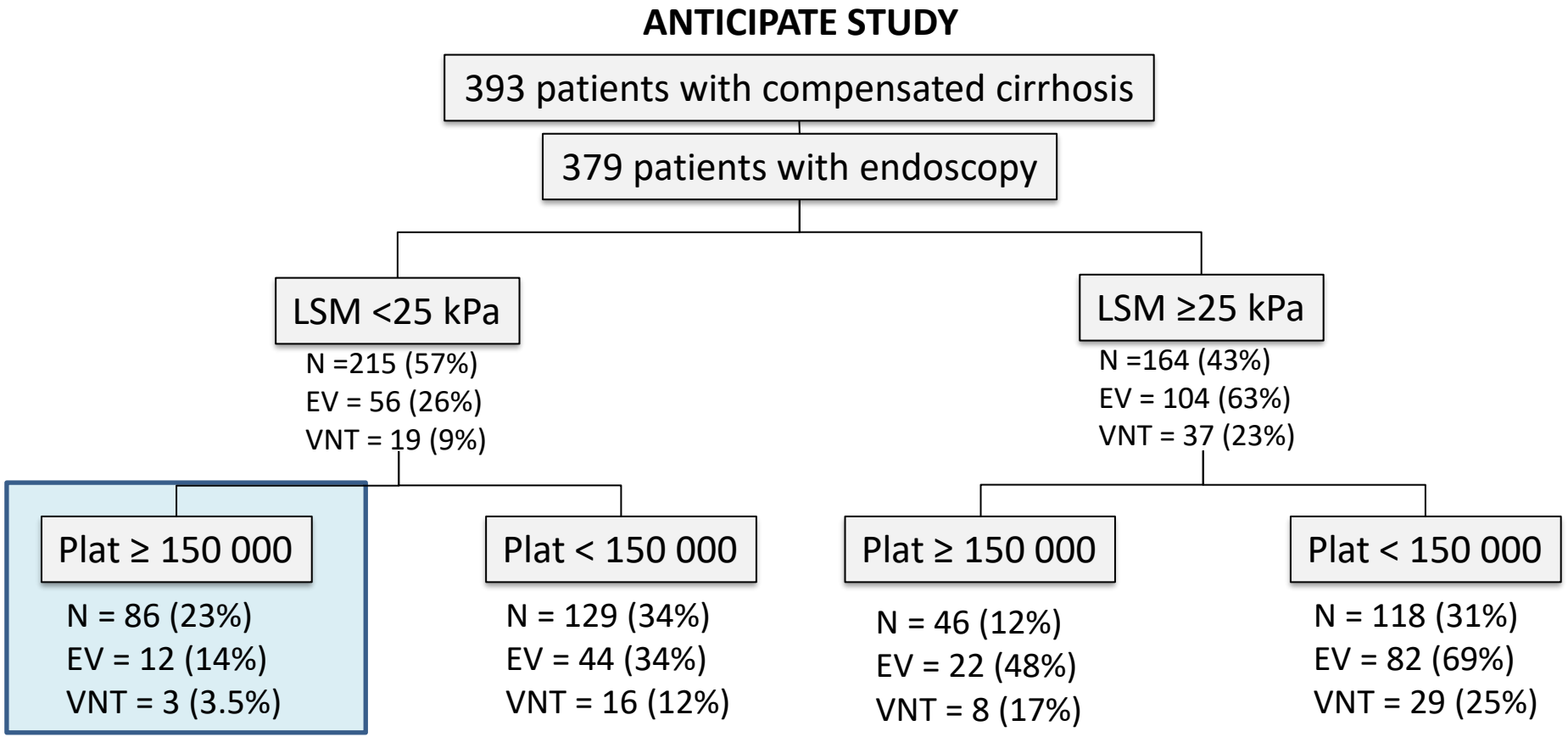






JG Abraldes, et al. Hepatology 2016

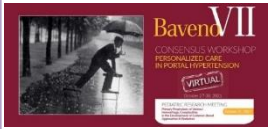
Elastography: varices-cACLD



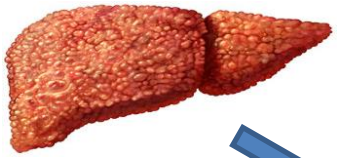
Baveno VI-2015-elastography: avoiding endoscopic screening varices

- **Patients with LSM <20 kPa and platelets >150000 can avoid screening endoscopy**
- **They should be followed up yearly with LSM/platelets**
- **Changes should promt endoscopy**
- **Risk of missing VNT: <5%**

For patients not starting NSBB



Compensated disease



Transient elastography & Platelets

LSM <20 kPa *AND* Platelets >150

FOLLOW UP Repeat yearly

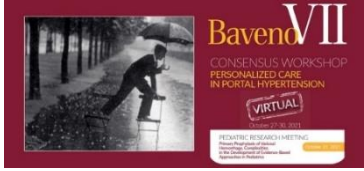
LSM ≥20 kPa *OR* Platelets ≤150

ENDOSCOPY

Decompensated disease

Vall d'Hebron Barcelona Campus Hospitalari

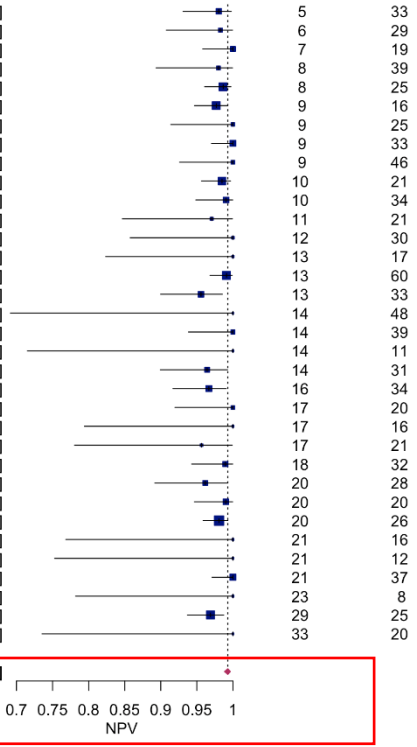
Performance of Baveno VI



Overall

Study	NPV	95% C.I.	Prev of HRV (%)	% Saved
Maurice et al, 2016	0.98	[0.93; 1.00]	5	33
Kotwal et al, 2020 Validation cohort	0.98	[0.91; 1.00]	6	29
Tosetti et al, 2019	1.00	[0.96; 1.00]	7	19
Nawalerspanya et al, 2018	0.98	[0.89; 1.00]	8	39
Thabut et al, 2019	0.99	[0.96; 1.00]	8	25
Calvaruso et al, 2019	0.98	[0.95; 0.99]	9	16
Jangouk et al, 2016 (US)	1.00	[0.91; 1.00]	9	25
Kotwal et al, 2020 Development cohort	1.00	[0.97; 1.00]	9	33
Sousa et al, 2017	1.00	[0.93; 1.00]	9	46
Augustin et al, 2017	0.98	[0.96; 1.00]	10	21
Petta et al, 2018 Training cohort M probe	0.99	[0.95; 1.00]	10	34
Bellan et al, 2018	0.97	[0.85; 1.00]	11	21
Moctezuma-Velazquez et al, 2019 PSC group	1.00	[0.86; 1.00]	12	30
Colecchia et al, 2018 Prospective cohort	1.00	[0.82; 1.00]	13	17
Matsui et al, 2018	0.99	[0.97; 1.00]	13	60
Petta et al, 2018 Validation cohort M probe	0.96	[0.90; 0.99]	13	33
Galizzi et al, 2021	1.00	[0.69; 1.00]	14	48
Moctezuma-Velazquez et al, 2019 PBC group	1.00	[0.94; 1.00]	14	39
Silva et al, 2017	1.00	[0.72; 1.00]	14	11
Wong et al, 2019	0.96	[0.90; 0.99]	14	31
Kew et al, 2020	0.97	[0.92; 0.99]	16	34
Cales et al, 2018	1.00	[0.92; 1.00]	17	20
Jangouk et al, 2016 (IT)	1.00	[0.79; 1.00]	17	16
Petta et al, 2018 BMI<30 M probe	0.96	[0.78; 1.00]	17	21
Gaete et al, 2020	0.99	[0.94; 1.00]	18	32
Bae et al, 2018	0.96	[0.89; 0.99]	20	28
Colecchia et al, 2018 Retrospective cohort	0.99	[0.95; 1.00]	20	20
Lee et al, 2018	0.98	[0.96; 0.99]	20	26
Duan et al, 2020 Beijing cohort	1.00	[0.77; 1.00]	21	16
Protopapas et al, 2020	1.00	[0.75; 1.00]	21	12
Wang et al, 2020	1.00	[0.97; 1.00]	21	37
Stefanescu et al, 2019	1.00	[0.78; 1.00]	23	8
Sharma et al, 2020	0.97	[0.94; 0.99]	29	25
Stanislas et al, 2018	1.00	[0.74; 1.00]	33	20
Pooled NPV (random effects)	**0.99**	**[0.99; 1.00]**		

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.69$



By Etiology

Study	NPV	95% C.I.	Prev of HRV (%)	% Saved
Etiology = Hepatitis B				
Bae et al, 2018	0.93	[0.83; 0.99]	20	25
Lee et al, 2018	0.96	[0.91; 0.99]	20	25
Stanislas et al, 2018	1.00	[0.86; 1.00]	33	20
Souza et al, 2017	1.00	[0.50; 1.00]	0	75
Wang et al, 2020	1.00	[0.99; 1.00]	21	37
Pooled NPV (random effects)	**1.00**	**[0.99; 1.00]**		

Heterogeneity: $I^2 = 64\%$, $\tau^2 = 0$, $\chi^2_4 = 11.09$ ($p = 0.03$)

Etiology = Hepatitis C				
Bae et al, 2018	1.00	[0.85; 1.00]	4	24
Bellan et al, 2018	0.97	[0.88; 1.00]	11	21
Calvaruso et al, 2019	0.98	[0.95; 0.99]	9	16
Lee et al, 2018	1.00	[0.96; 1.00]	14	27
Souza et al, 2017	1.00	[0.96; 1.00]	10	48
Pooled NPV (random effects)	**0.99**	**[0.98; 1.00]**		

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\chi^2_4 = 2.09$ ($p = 0.72$)

Etiology = Alcohol				
Bae et al, 2018	1.00	[0.87; 1.00]	30	25
Lee et al, 2018	0.99	[0.94; 1.00]	25	20
Maurice et al, 2016	1.00	[0.89; 1.00]	2	38
Souza et al, 2017	1.00	[0.50; 1.00]	8	25
Pooled NPV (random effects)	**1.00**	**[0.98; 1.00]**		

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\chi^2_3 = 0.22$ ($p = 0.97$)

Etiology = NAFLD				
Bae et al, 2018	1.00	[0.86; 1.00]	6	71
Gaete et al, 2020	0.99	[0.94; 1.00]	19	37
Galizzi et al, 2021	1.00	[0.83; 1.00]	14	48
Maurice et al, 2016	1.00	[0.90; 1.00]	5	77
Petta et al, 2018 NAFLD (Training cohort, M)	0.99	[0.96; 1.00]	10	34
	0.96	[0.91; 0.99]	13	33
Petta et al, 2018 NAFLD BMI <30 M probe	0.96	[0.82; 1.00]	17	21
Pooled NPV (random effects)	**0.99**	**[0.97; 1.00]**		

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\chi^2_6 = 3.46$ ($p = 0.75$)

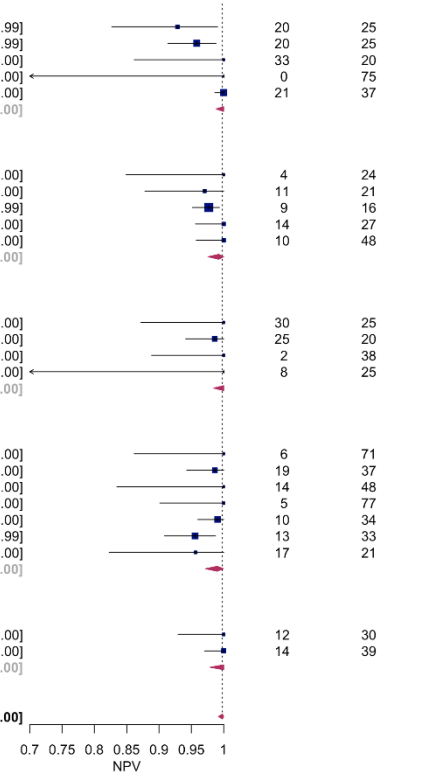
Etiology = Cholestatic				
Moctezuma et al. 2019 PSC	1.00	[0.93; 1.00]	12	30
Moctezuma et al. 2019 PBC	1.00	[0.97; 1.00]	14	39
Pooled NPV (random effects)	**1.00**	**[0.98; 1.00]**		

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\chi^2_1 = 0.09$ ($p = 0.77$)

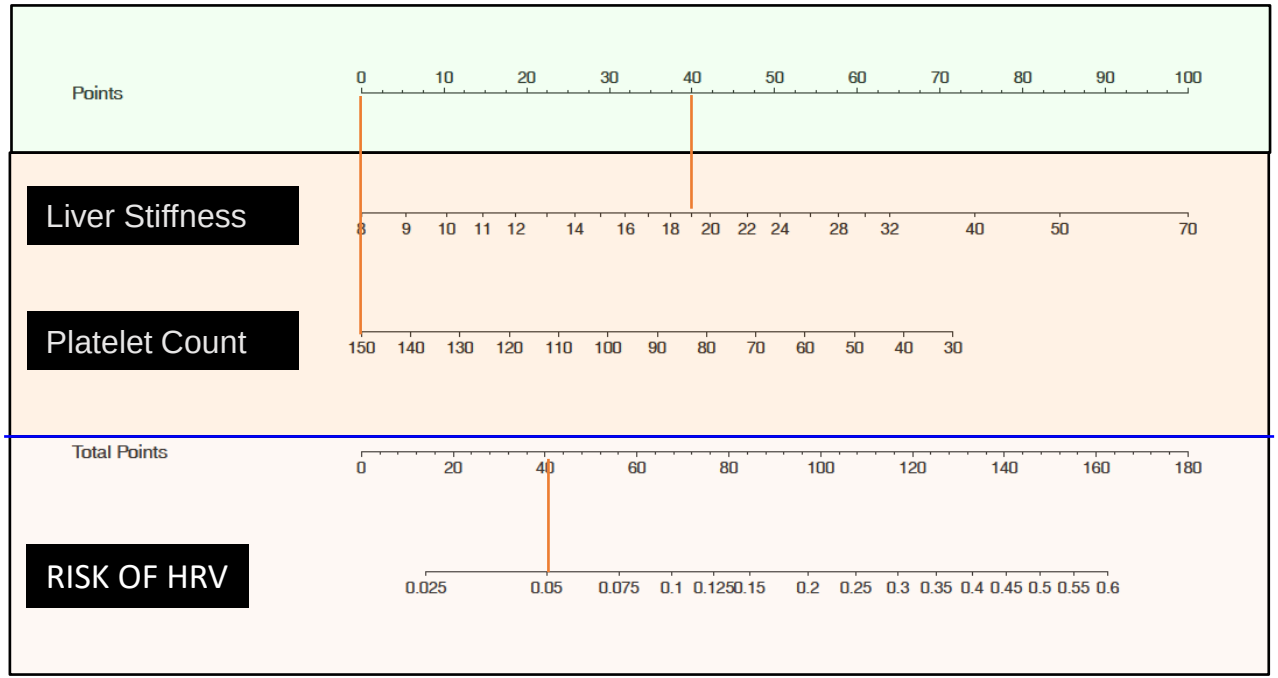
Pooled NPV (random effects)	**1.00**	**[0.99; 1.00]**		

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\chi^2_{22} = 19.16$ ($p = 0.64$)

Test for subgroup differences: $\chi^2_4 = 2.21$, df = 4 ($p = 0.70$)



Prediction of Varices Needing Treatment
TE + Platelet count



Baveno VI criteria: LSM by TE >20 kPa OR Platelet count <150

Maximum risk of VNT: 5%

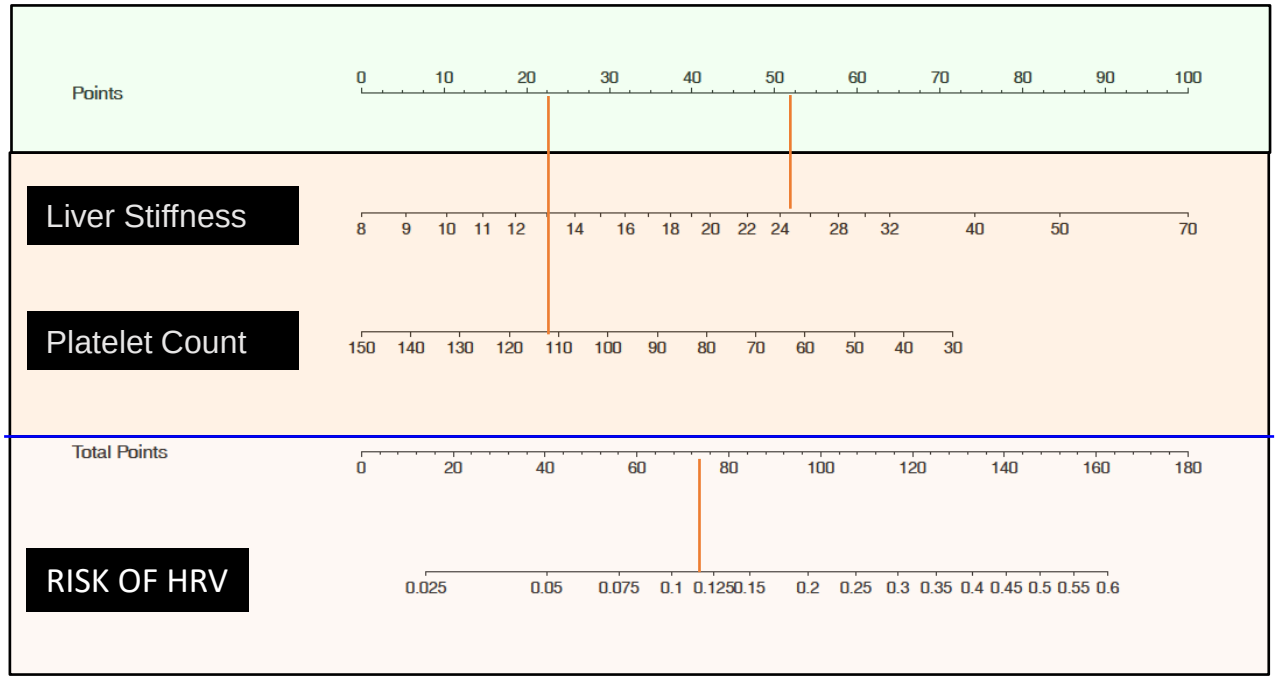
NEW CRITERIA-VALIDATION-ETIOLOGIES

PLA>110+LSM<25

ETIOLOGY	No EGD	HRV/ Expanded Baveno VI	HRV/ All
HCV	236/584 (40%)	3/236 (1.2%)	3/584 (0.5%)
Alcohol	49/127 (38.5%)	0/49	0/127
NASH	44/90 (49%)	1/44 (2.2%)	1/90 (1.1%)
HBV	21/61 (34.4%)	1/21 (4.7%)	1/61 (1.6%)
PBC/PBS	12/20 (60%)	1/12 (8.3%)	1/20 (5%)
HCV/Alcohol	5/19 (26%)	0/5	0/19

Augustin, et al. Hepatology 2017

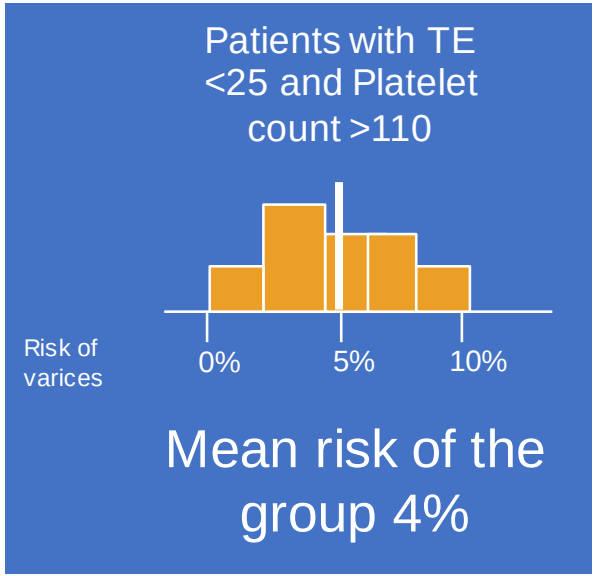
Risk of VNT
(Anticipate study, 2016, Hepatology)

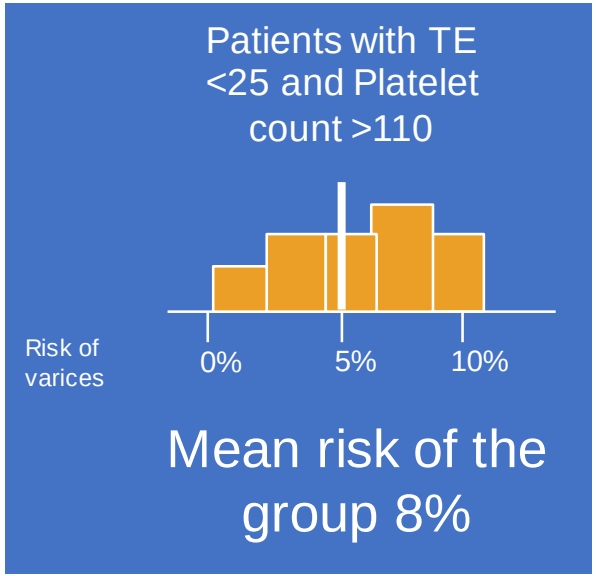


Expanded Baveno VI criteria: LSM by TE >25 OR Platelet count <110
(maximum risk of VNT ˜12%)

Expanded Baveno VI:

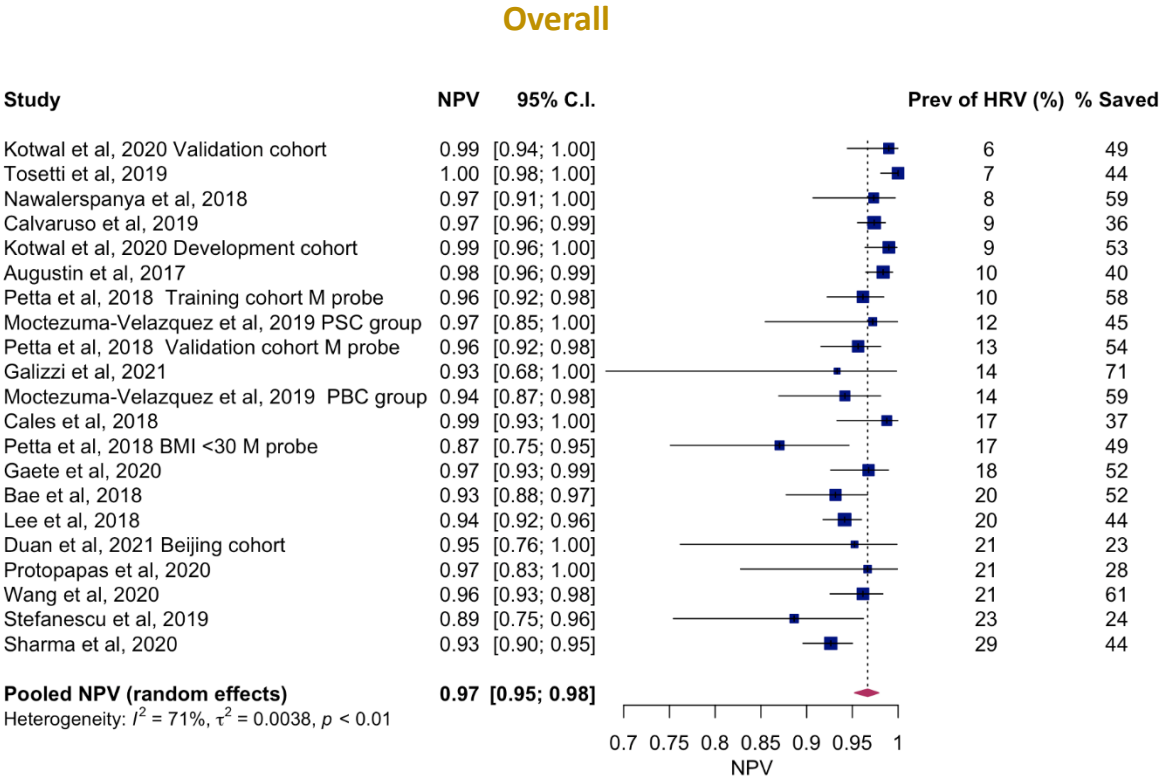
Patients within Baveno VI + **Patients beyond Baveno VI (LSM 20-25 kPa or Platelet 110-150)**





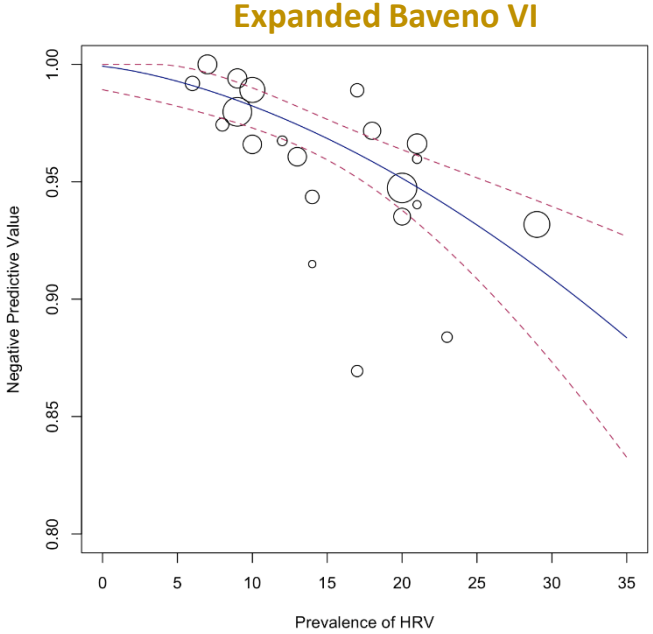
Series with patients at higher risk → higher prevalence of VNT → lower NPV

Performance of Expanded Baveno VI (risk up to ˜12%)



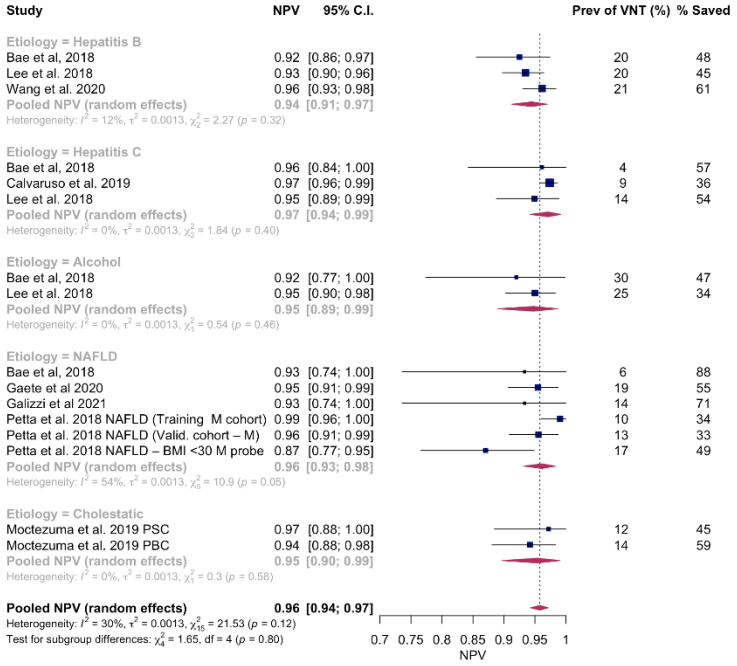
Influence of Prevalence of HRV and etiology on the performance of Baveno VI and Expanded Baveno VI criteria

Expanded Baveno VI



Meta-regression: prevalence explained 77% of observed heterogeneity in the NPV of Expanded Baveno VI (p<0.0001)

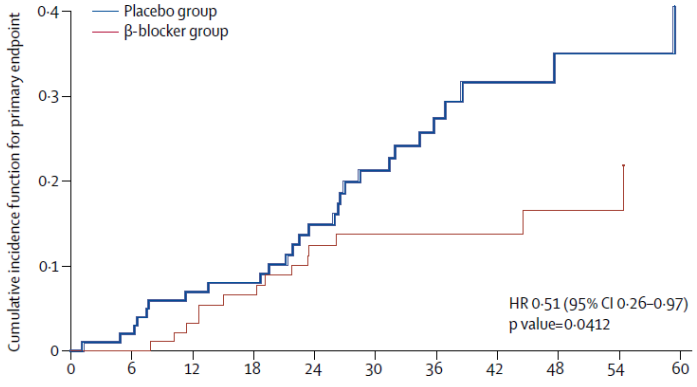
Expanded Baveno VI, by etiology



No significant variation in Expanded Baveno VI NPV by etiology (p=0.70)

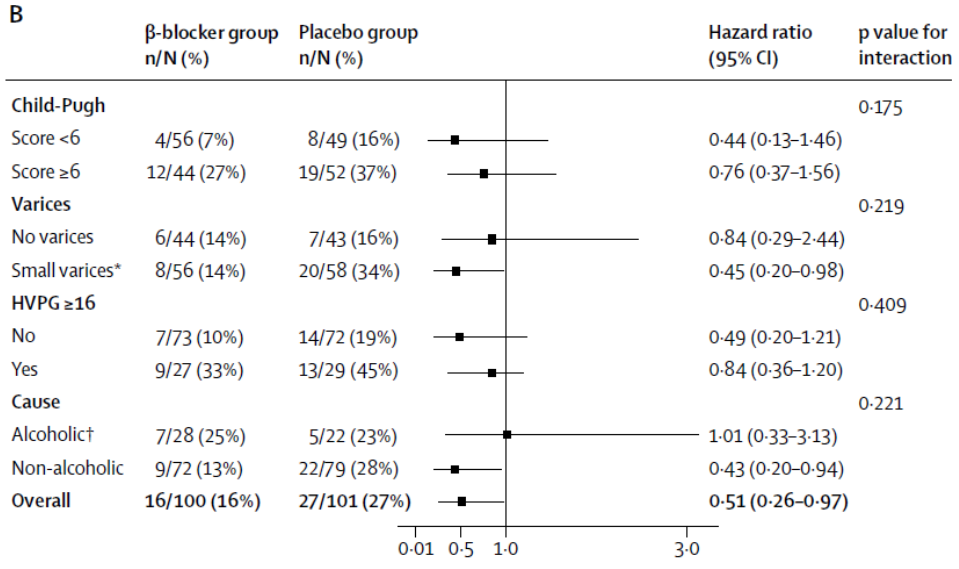
PREDESCI STUDY

A



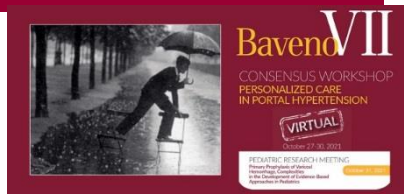
Patients at risk											
β blockers	100	96	87	80	69	60	48	31	20	15	7
Placebo	101	99	94	86	72	59	42	26	19	13	6
Primary outcome (deaths)											
β blockers		1 (1)	3 (1)	4 (2)	5 (2)	1 (1)	0	0	1 (1)	0	1
Placebo		2 (2)	5 (1)	1	6 (2)	5 (1)	4 (3)	2 (1)	1 (1)	0	1
Censoring events											
β blockers		3	6	3	6	8	12	17	10	5	7
Placebo		0	0	7	8	8	13	14	6	6	6

B



-Treatment with non-selective beta-blockers (propranolol, nadolol or carvedilol) is recommended for the prevention of decompensation in patients with CSPH (A1).
-Carvedilol is the preferred NSBB in compensated cirrhosis, since it is more effective in reducing HVPG (A1)…

Villanueva, et al. The Lancet 2019



Elastography: detecting CSPH

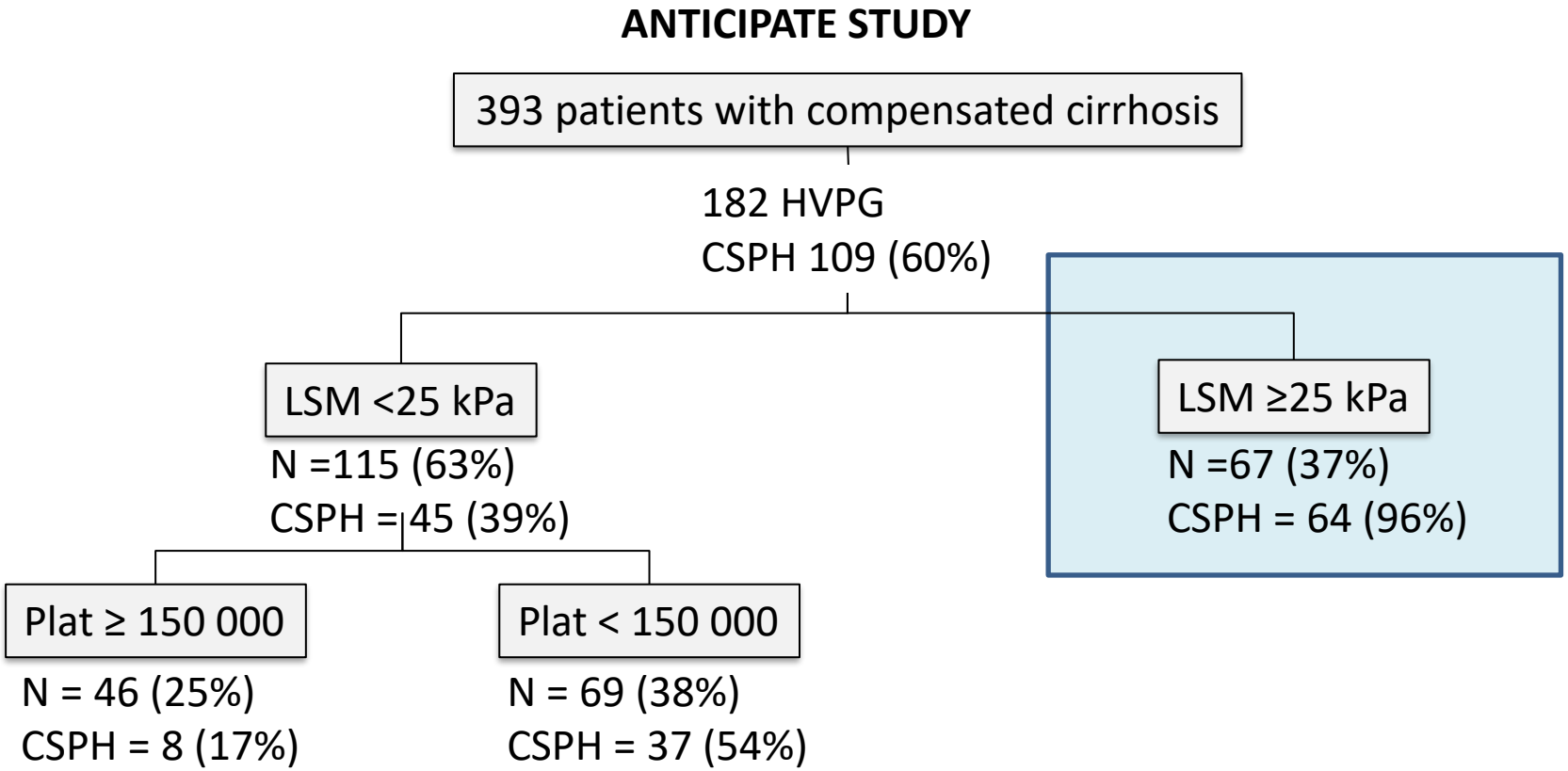


Table 2
Accuracy of LSM for the diagnosis of CSPH

Study, Year	Study Design	Population	Correlation Coefficient Between LSM and HVPG	AUROC for CSPH	Cut-off for CSPH	Sensitivity (%)	Specificity (%)
TE (only studies with ≥100 patients selected)							
Bureau et al,[18] 2008	Prospective	144 patients with HCV or alcoholic cirrhosis	0.858	0.945	21 kPa	89.9	93.2
Colecchia et al,[106] 2012	Prospective	100 patients with HCV cirrhosis	0.836	0.836	24.2 kPa	52.3	97.1
Reiberger et al,[143] 2012	Retrospective	502 patients with/without cirrhosis, some decompensated (mixed etiologies)	0.794	0.871	18 kPa	82.2	83.4
Schwabl et al,[144] 2015	Retrospective	188 patients with chronic liver disease	0.846	0.957	16.1 kPa	94.8	86.9
Cho et al,[145] 2015	Retrospective	219 patients with alcoholic cirrhosis (some decompensated)	n. a.	0.85	n. a.	n. a.	n. a.
Zykus et al,[146] 2015	Prospective	107 patients with cirrhosis (mixed etiologies)	0.750	0.949	17.4 kPa	88	87.5
Hametner et al,[147] 2015	Retrospective	236 patients with cirrhosis (mixed etiologies)	n. a.	0.92	24.8 kPa	81	93
Kumar et al,[148] 2017	Retrospective	326 patients with cirrhosis (mixed etiologies)	n. a.	0.74	21.46 kPa	79	67
Salavrakos et al,[60] 2018	Retrospective	118 patients with alcoholic liver disease	0.753	0.925	30.6 kPa	81	94

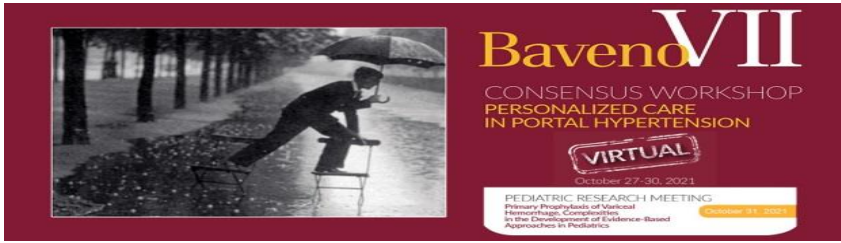
Vuille-Lessard et al., Clin Liver Dis 2021

Baveno VI-2015-elastography: detecting CSPH

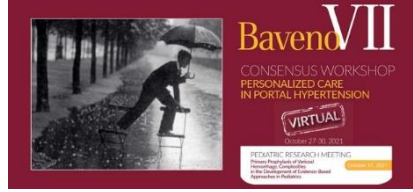
- **In virus-related cACLD non-invasive methods are sufficient to rule in CSPH**
- **LSM by TE ≥20-25 kPa alone or combined to platelets/spleen size**
- **In other etiologies remains to be ascertained**
- **Imaging showing collateral circulation rules in CSPH**

Vall d'Hebron
Barcelona Campus Hospitalari

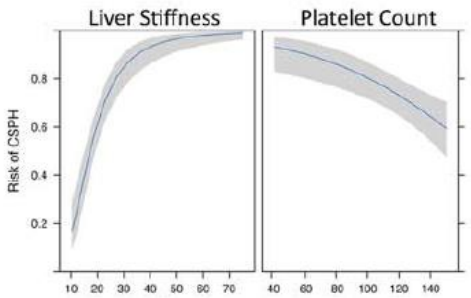
Baveno VI

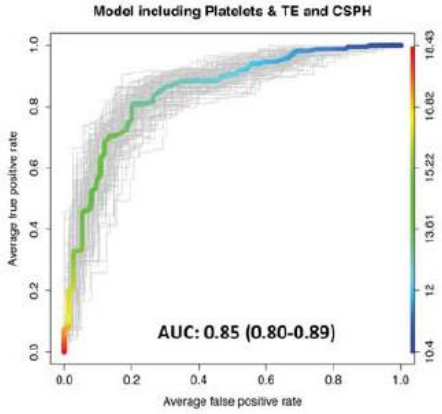


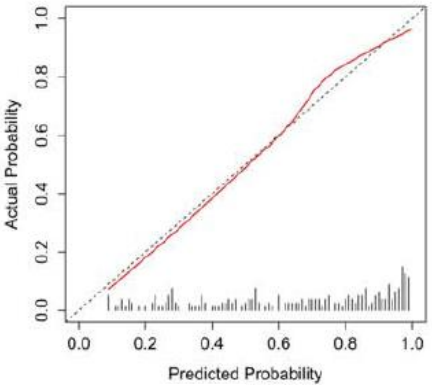
-Although the concept of CSPH is HVPG-driven, non-invasive tests are sufficiently accurate for estimating CSPH in clinical practice (A;1) (New)

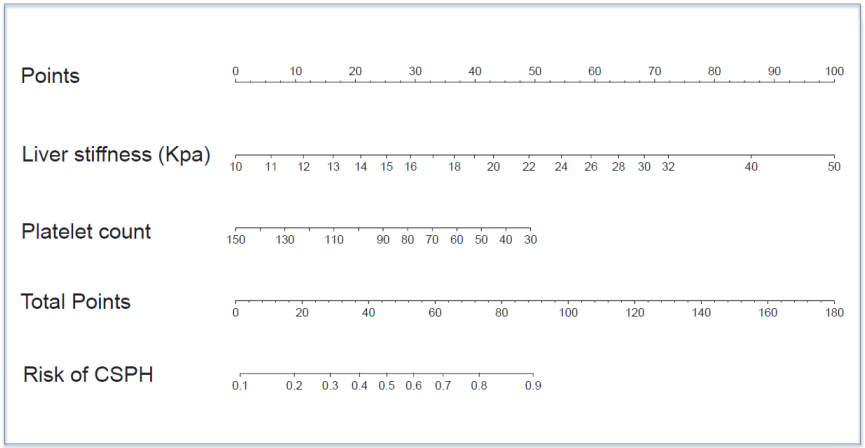


Liver Stiffness + Platelet count



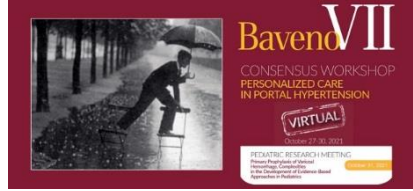


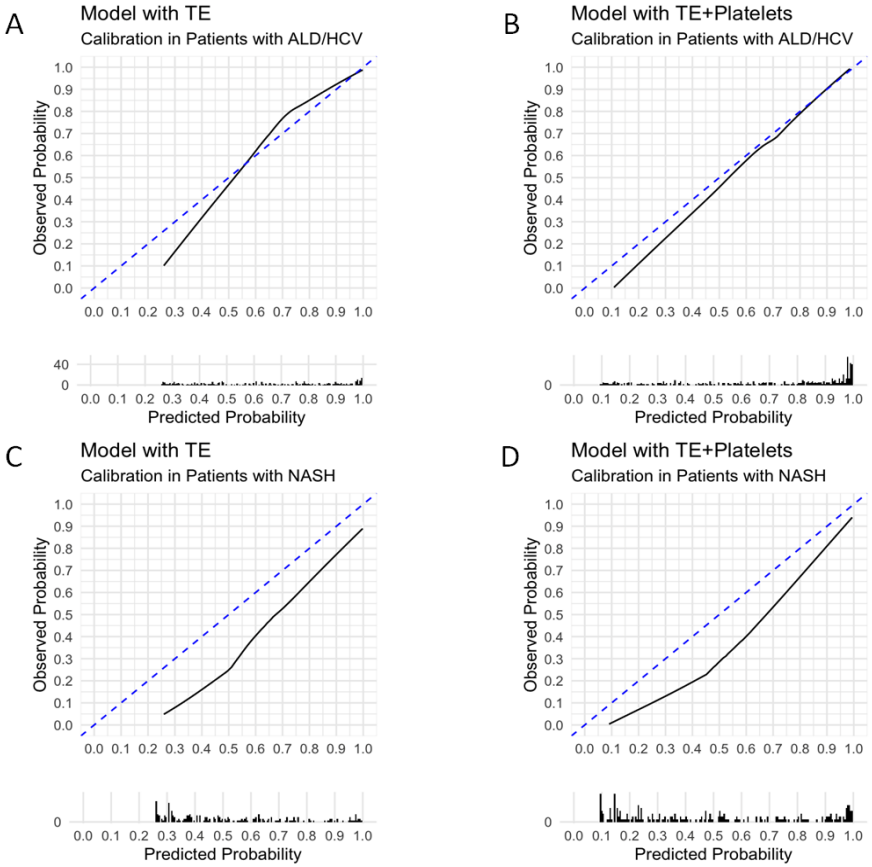




Risk prediction model for CSPH (virus/alcohol)

ANTICIPATE-Abraldes, et al. Hepatology 2016



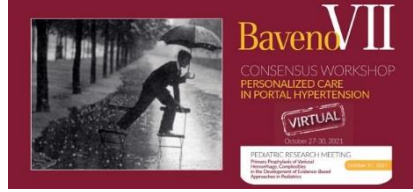


Validation of the ANTICIPATE model in another population (virus/alcohol)

Over prediction of the ANTICIPATE model in NASH patients

836 cACLD patients (virus/alcohol/NASH)

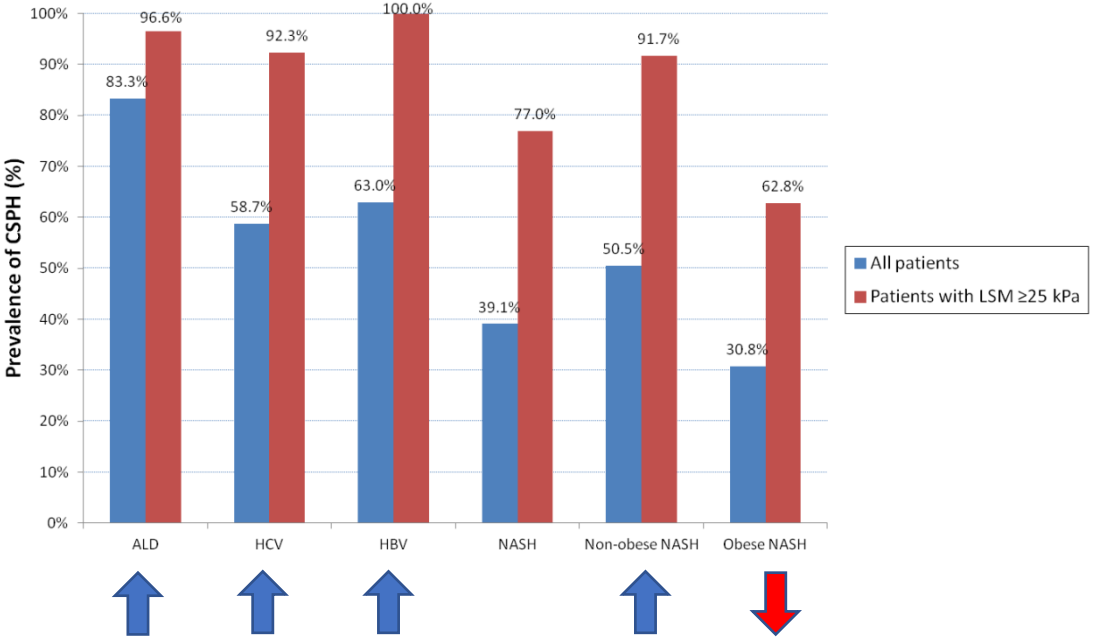
Pons, et al. AJG 2021

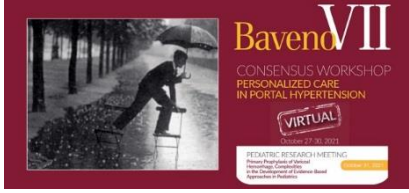


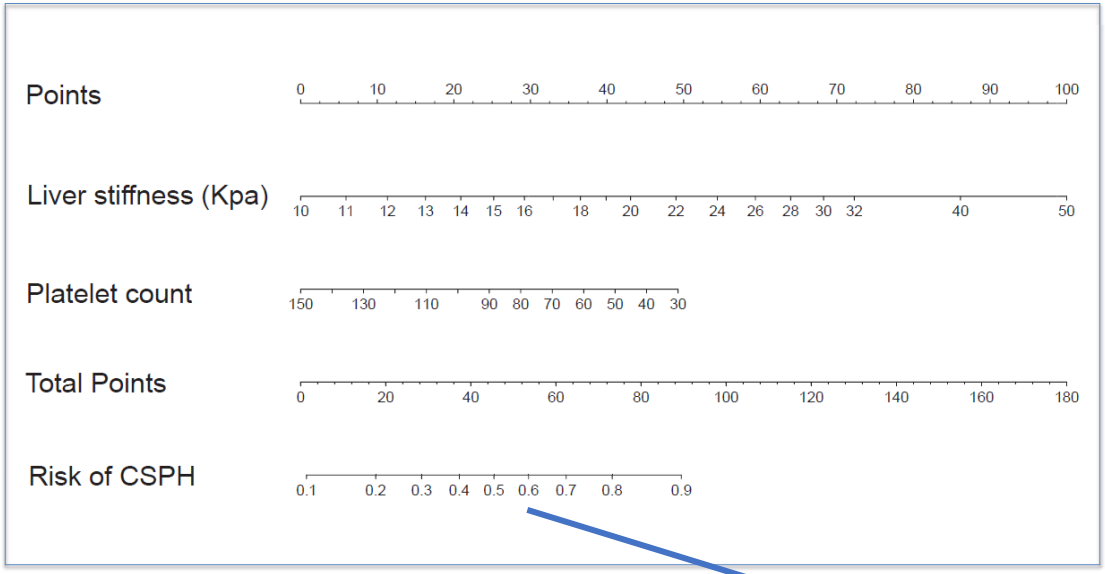
Pons, et al. AJG 2021

LSM≥25 kPa ruling in

(>90% PPV, >90% Sp)







Risk prediction model for CSPH (virus/alcohol)

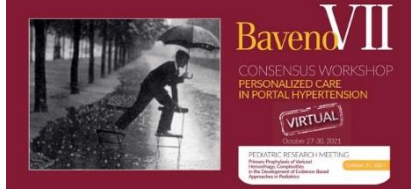
CSPH risk of at least 60%:

-LSM between 20-25 kPa and platelet count <150x10^9/L.

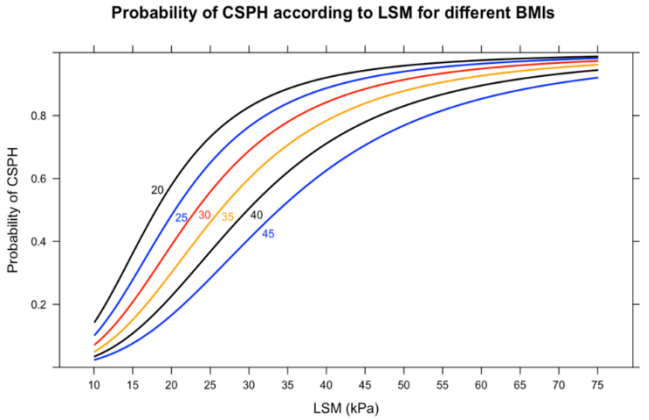
-LSM between 15-20 kPa and platelet count < 110x10^9/L.

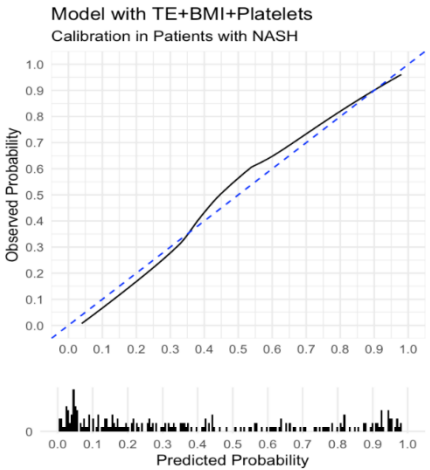
Pons, et al. AJG 2021

Abraldes, et al. Hepatology 2016

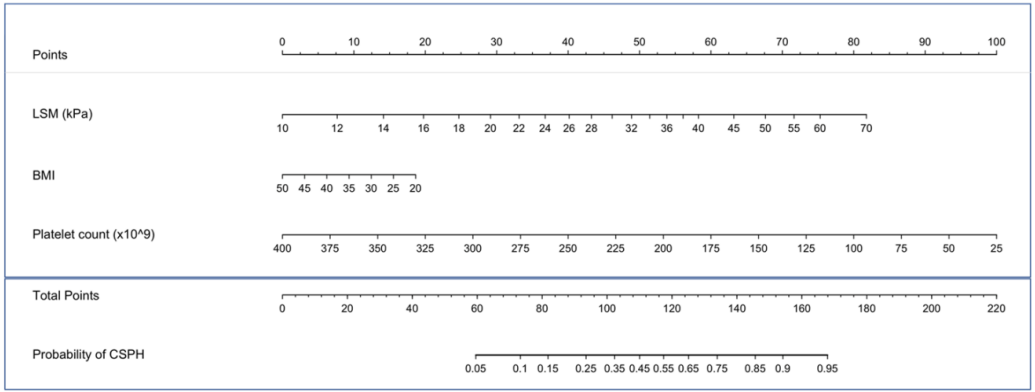


Pons, et al. AJG 2021





New ANTICIPATE-NASH model



Pons, et al. AJG 2021

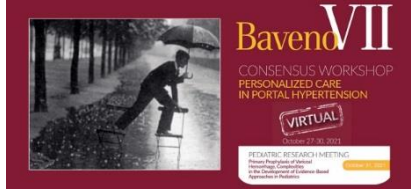
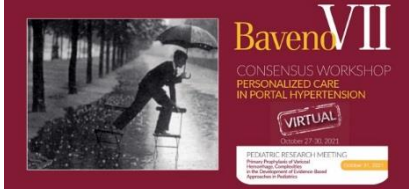


Table 3. Negative predictive value (NPV) of different LSM cutoffs and also adding platelet count to rule out the presence of CSPH in different etiologies

LSM cutoff	Etiology	No. of patients[a]	HVPG <10 mm Hg[b]	NPV (95% CI)
<15 kPa	ALD	23	17	73.9 (53.5–87.5)
	HCV	87	71	81.6 (72.2–88.4)
	NASH	85	75	88.2 (79.7–93.5)
	HBV	8	5	62.5 (30.6–86.3)
	All	203	168	82.8 (77–87.3)
<13.6 kPa	ALD	16	11	68.8 (44.4–85.8)
	HCV	63	54	85.7 (75–92.3)
	NASH	64	57	89.1 (79.1–94.6)
	HBV	5	4	80 (37.6–96.4)
	All	148	126	85.1 (78.5–90)
≤15 kPa + platelets ≥150 × 10^9/L	ALD	12	12	100 (75.8–100)
	HCV	34	34	100 (89.8–100)
	NASH	66	63	95.5 (87.5–98.4)
	HBV	5	4	80 (37.6–96.4)
	All	117	113	96.6 (91.5–98.7)

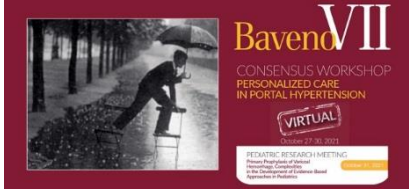
SP >90%

ALD, alcoholic liver disease; CI, confidence interval; HBV, chronic hepatitis B; HCV, chronic hepatitis C; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; NASH, nonalcoholic steatohepatitis.
[a]Number of patients within LSM cutoff.
[b]Number of patients without clinically significant portal hypertension within the LSM cutoff.



Identification of patients with chronic liver disease (viral and alcoholic etiology) at risk of CSPH in the different stages of the disease by using noninvasive tests including liver stiffness.

	STAGES OF CHRONIC LIVER DISEASE						
	No cirrhosis		Early compensated cirrhosis	Late compensated cirrhosis			Decompensated cirrhosis
	CLD	Early cACLD		Late cACLD			dACLD
Liver fibrosis	F1-F2	F3	F4	F4			F4
HVPG (mm Hg)	<5	5 - <10		≥10			≥10
Portal hypertension	No	Mild		CSPH			CSPH
Liver stiffness (kPa)	<10	10-<25		15 - <20	20 - <25	≥25	Unneeded
Platelet count (K/mm^3)	Any	Normal		<110	<150	Any	Any



Session 1: Evaluation and risk stratification

Part 2: Noninvasive tools for cACLD and portal hypertension

Clinically significant portal hypertension (CSPH)

-CSPH: ≥25 kPa ruling in for viral/alcohol and non-obese NASH (>90% PPV, >90% Sp).

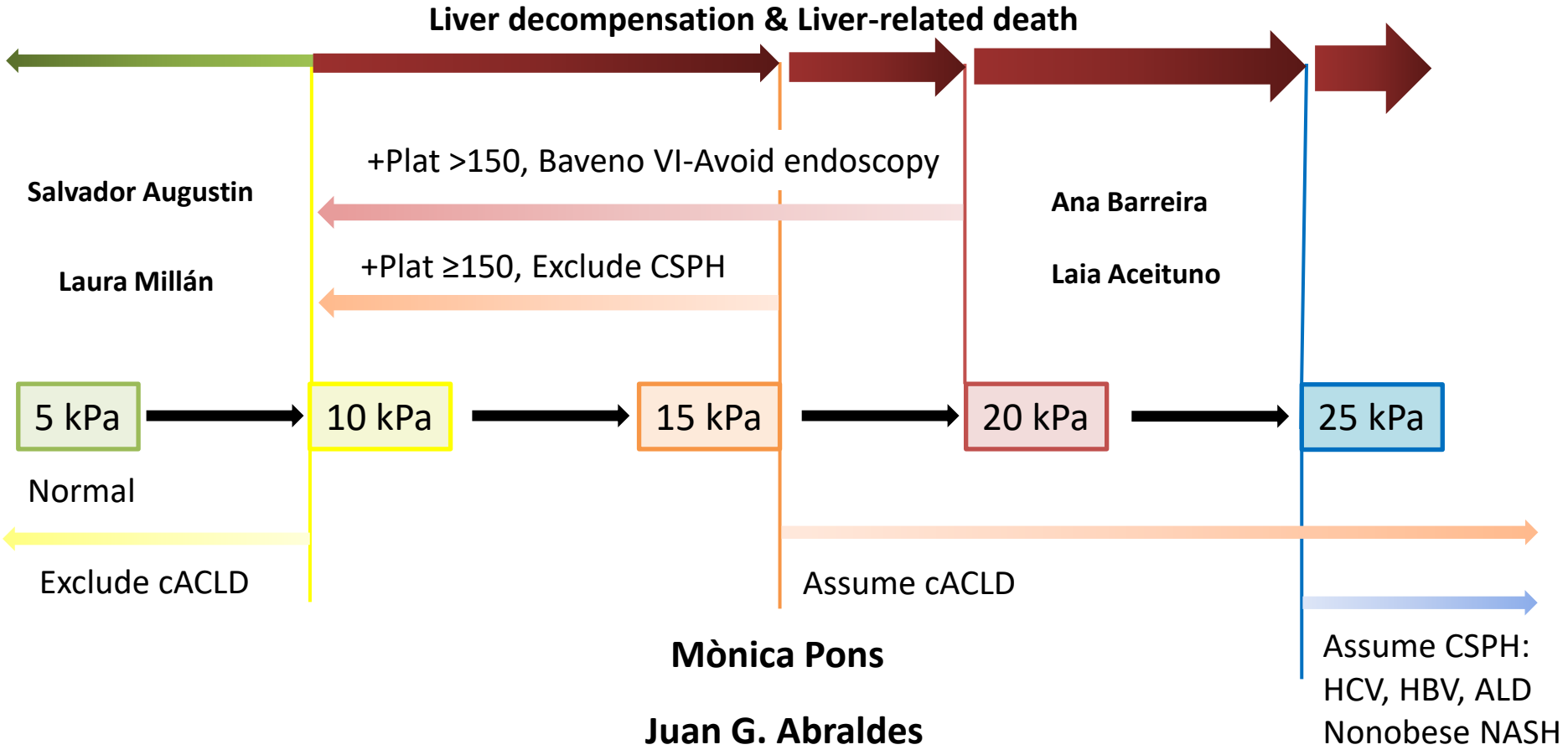
-CSPH: <25 kPa ANTICIPATE model for viral/alcohol (CSPH risk of at least 60%):

  -LSM between 20-25 kPa and platelet count <150x10^9/L.

  -LSM between 15-20 kPa and platelet count < 110x10^9/L.

-CSPH for NASH: NASH-ANTICIPATE model: see table with practical examples based on model prediction.

-Ruling out CSPH: ≤15 kPa + pla ≥150 (>90% NPV, >90% Se).



Non-invasive prediction in cACLD by TE-summary: THE RULE OF FIVE

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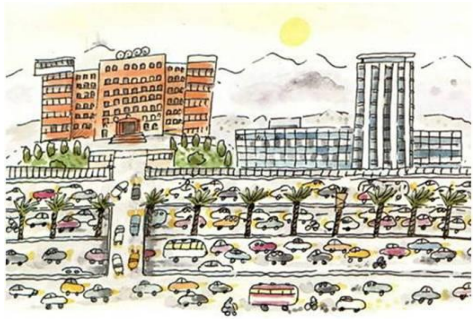

GRACIAS