MÁSTER EN HEPATOLOGÍA

Universidad Autónoma de Madrid

Universidad de Alcalá

Asignatura: Cirrosis I

“Elastografía de transición en el diagnóstico, seguimiento y pronóstico de la enfermedad hepática crónica”

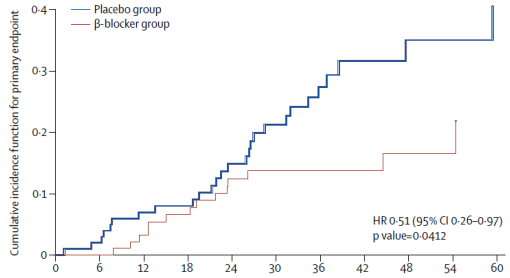
Joan Genescà

Servicio de Hepatología, Hospital Universitari Vall d’Hebron, Barcelona

LIVER STIFFNESS-TRANSIENT ELASTOGRAPHY

2008

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

2010-2013
PREDESCI
patient inclusion

OUTLINE

A little bit about...

-cACLD

-Prediction of outcomes

-Regression

-Varices

-CSPH

NO

-Prevention decompensation

-No other devices for LSM than TE

LIVER STIFFNESS-DETECCTION OF cACLD

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

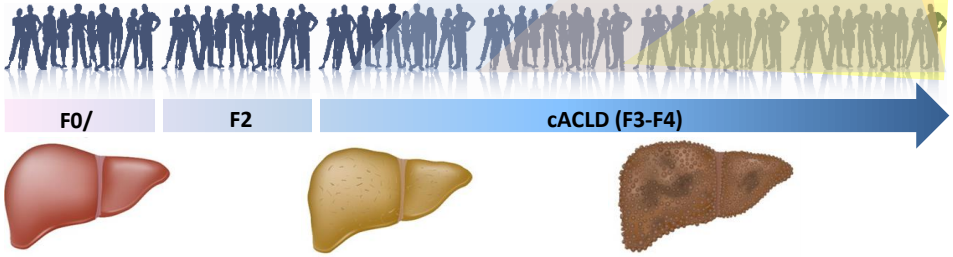
Point-of-care
Applicability
Easiness
Repeatable
Rapidness

TRANSIENT ELASTOGRAPHY

LIVER BIOPSY

CLINICAL DIAGNOSIS

CHRONIC LIVER DISEASE



LSM-EVALUATION OF CLD PATIENTS-cACLD

A pragmatic definition of cACLD based on liver stiffness measurement (LSM) is aimed at stratifying the risk of CSPH and decompensation at point of care, irrespective of histological stage or the ability of LSM to identify these stages.

LOW RISK OF F3-F4/PH/LRE

HIGH RISK OF F3-F4/PH/LRE

Normal

LSM kPa

cACLD

Cirrosis

5 **10** **15** **20** **25**

compensated Advanced Chronic Liver Disease

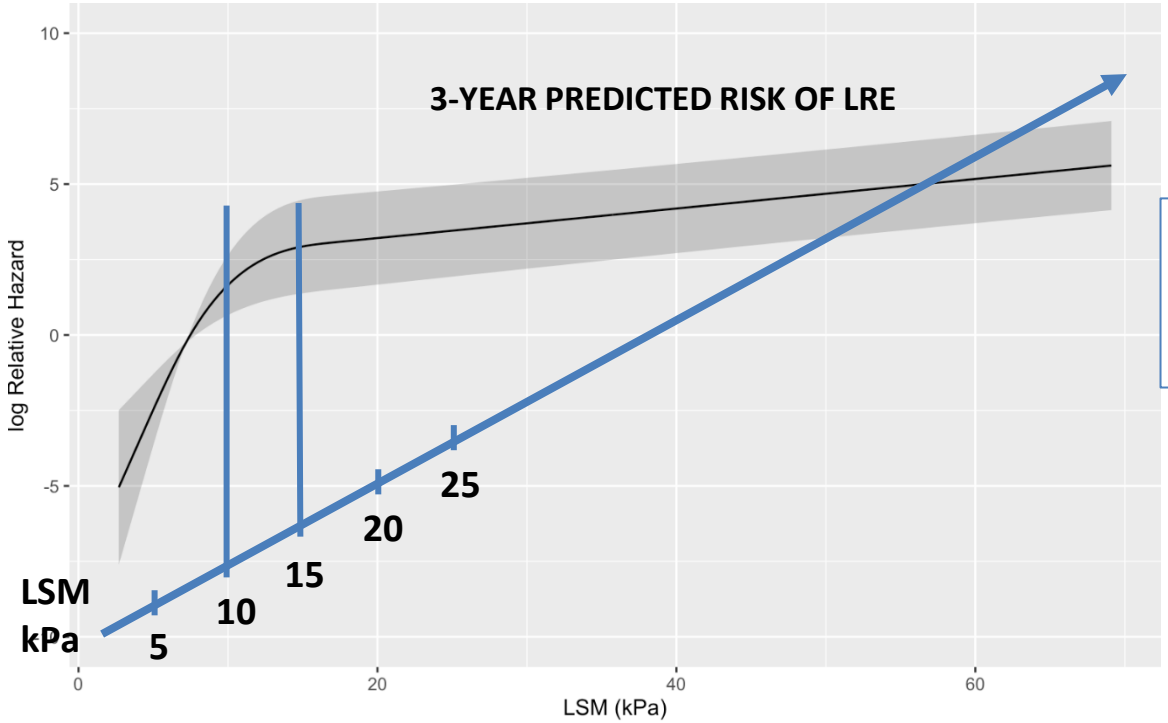
LSM <10 kPa-RISK OF LRE-MIXED PATIENTS

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

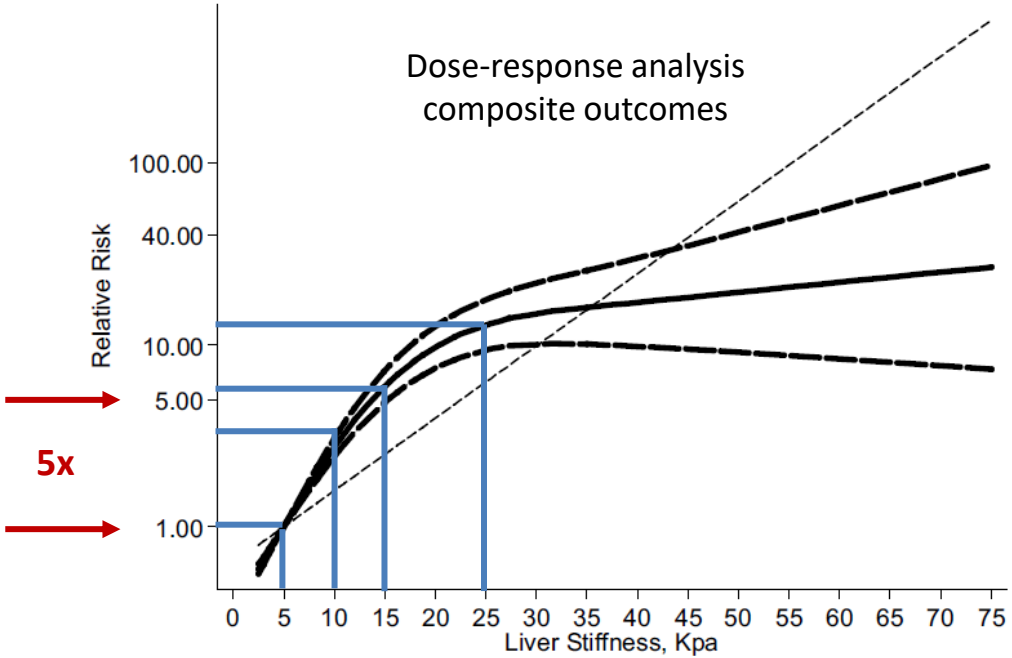
LSM-RISK OF LRE-NAFLD/NASH PATIENTS



-HUVH
-Canada
-France-Ledinghen
-Hong-Kong-Wong
-Multicenter-Petta

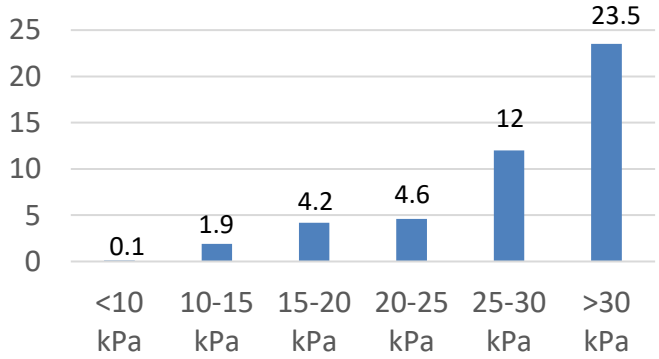
LSM-RISK OF LRE-MIXED PATIENTS

Systematic review and meta-analysis of outcomes and index LSM by TE
62 studies and 43,817 participants



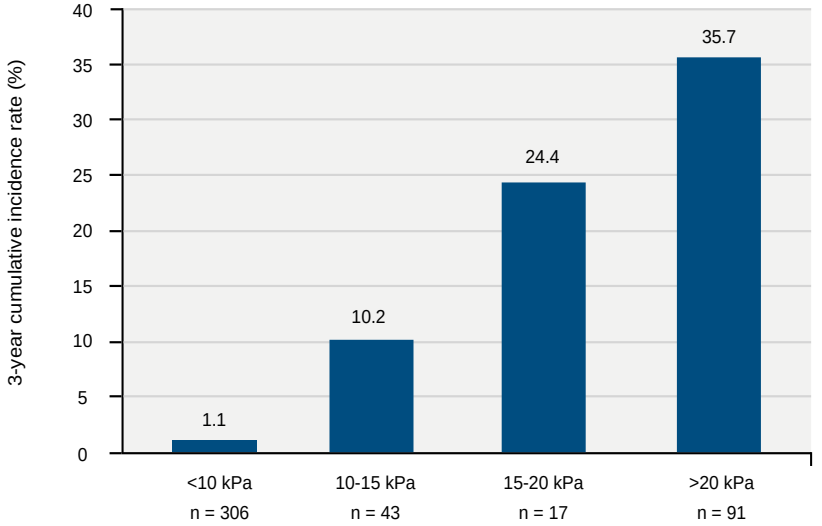
Shen, et al. H Int 2019

LSM-RISK OF LRE-NAFLD/NASH-ARLD PATIENTS



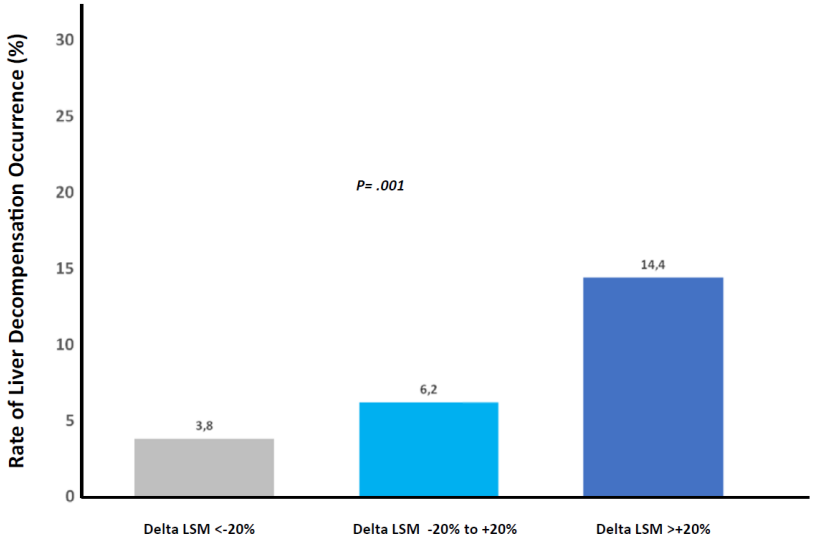
-HUVH
-Canada
-France-Ledinghen
-Hong-Kong-Wong
-Multicenter-Petta

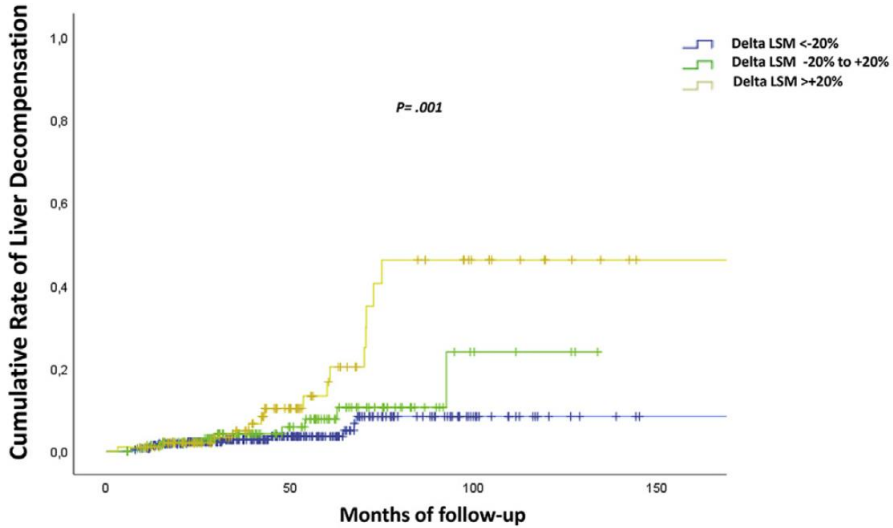
3-year cumulative incidence rate for LRE



316 patients (Denmark) with ARLD
(Rasmussen, JHep 2021)

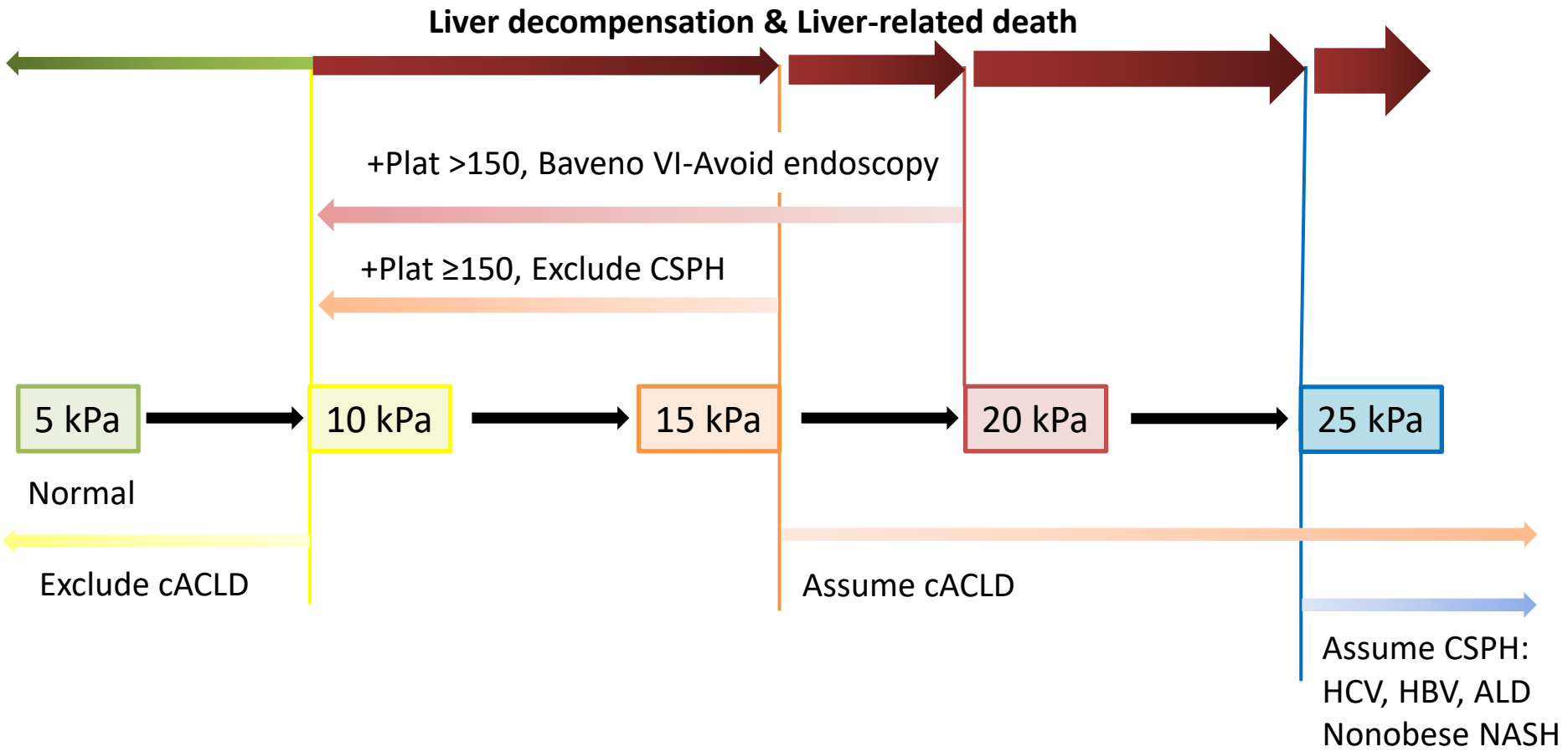
LSM REPETITIONS-RISK OF LRE-NAFLD/NASH PATIENTS



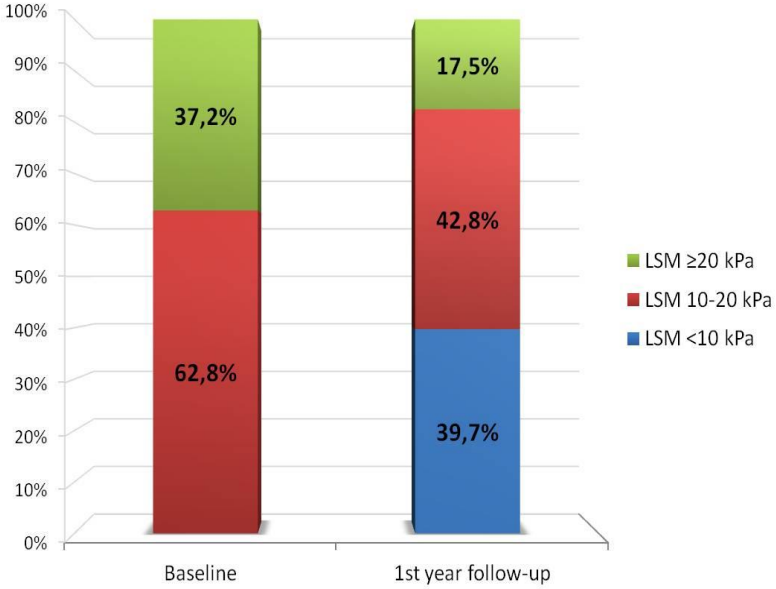


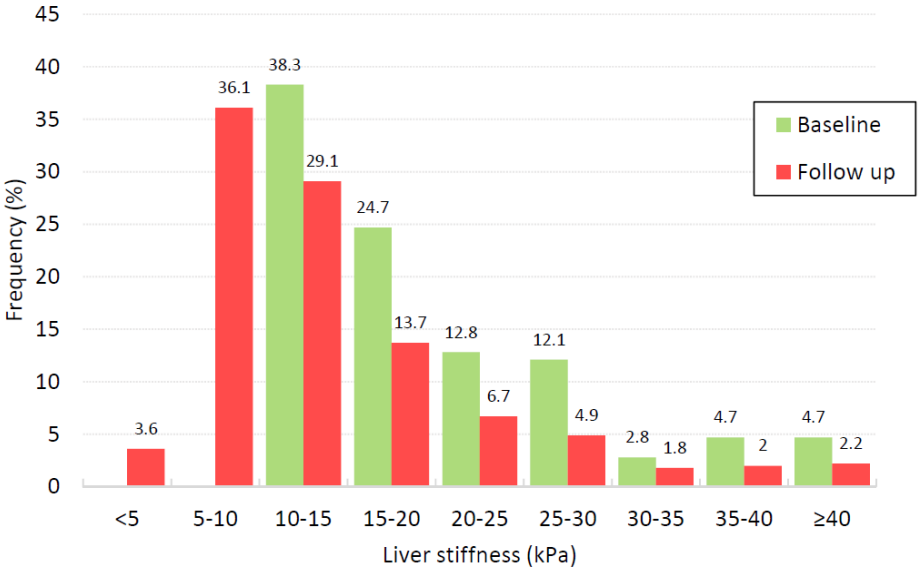
Petta, et al. CGH 2021

RULE OF 5


Liver decompensation & Liver-related death
+Plat >150, Baveno VI-Avoid endoscopy
+Plat ≥150, Exclude CSPH
5 kPa
10 kPa
15 kPa
20 kPa
25 kPa
Normal
Exclude cACLD
Assume cACLD
Assume CSPH:
HCV, HBV, ALD
Nonobese NASH

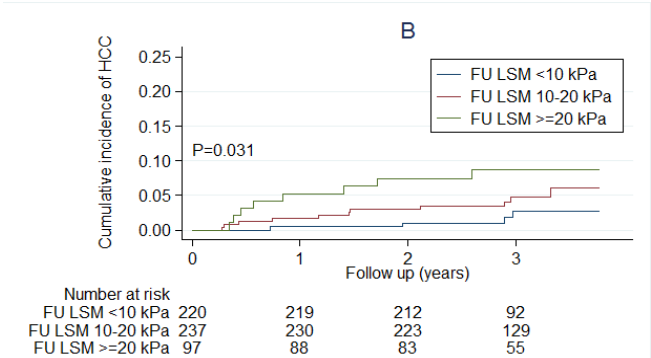
LSM-REGRESSION HCV-CURED PATIENTS

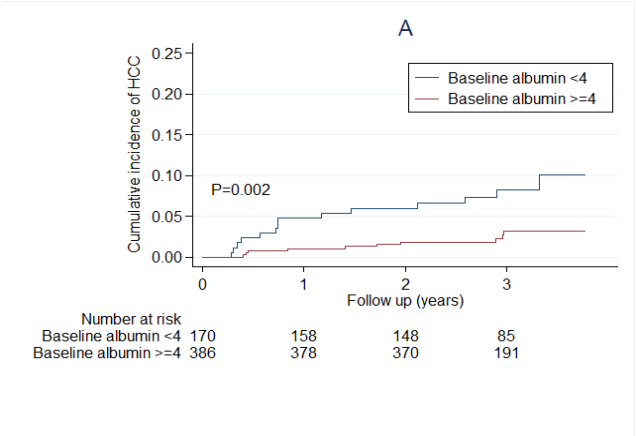


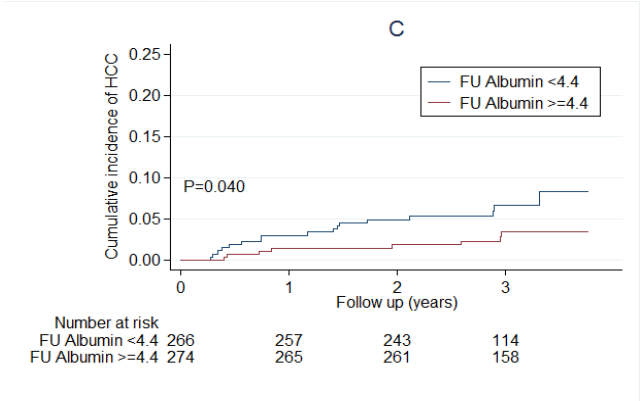


Pons, et al. J Hepatol 2020

LSM-REGRESSION HCV-CURED PATIENTS

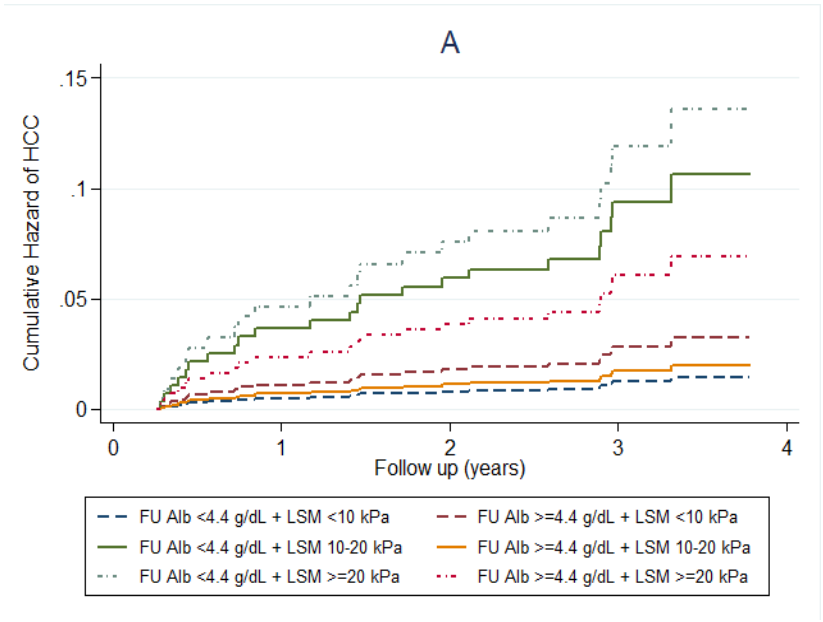


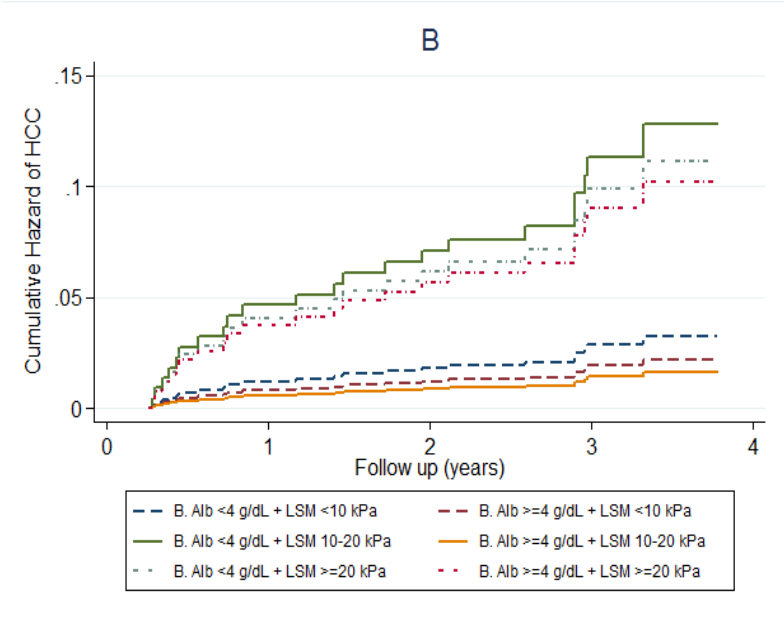




Pons, et al. J Hepatol 2020

LSM-REGRESSION HCV-CURED PATIENTS



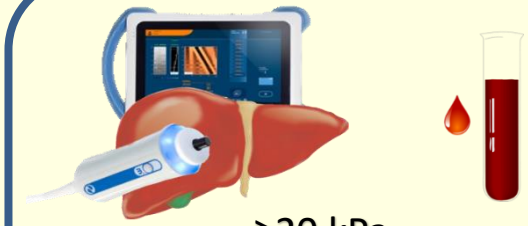


Pons, et al. J Hepatol 2020

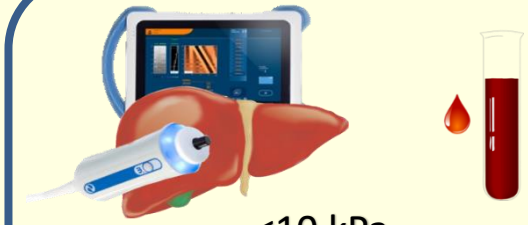
HCV
oral antiviral
therapy

SVR

Follow-up non-invasive tests

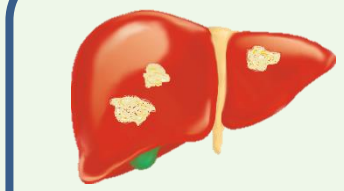


≥20 kPa
or
10-20 kPa + Albumin <4.4 g/dL

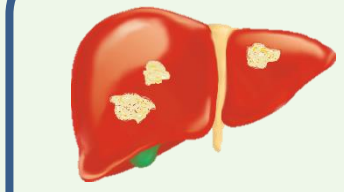


<10 kPa
or
10-20 kPa + Albumin ≥4.4 g/dL

HCC incidence rates



≥1.9/100 patient-years



<1/100 patient-years

Pons, et al. J Hepatol 2020

Pooled analysis

418 patients with paired HVPG-measurements +/- NIT before and after HCV-cure

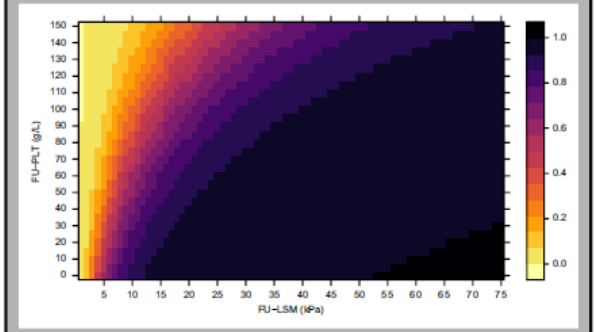
! Etiological cure modifies relationship between NIT and HVPG !

- Increased correlation LSM/HVPG
- Numerically higher accuracy for diagnosing CSPH

Clinical decision rules

LSM <12 kPa & PLT >150 G/L
→ CSPH excluded

Estimated probability of CSPH



LSM ≥25 kPa
→ CSPH ruled-in

Validation *vs.* Direct endpoints

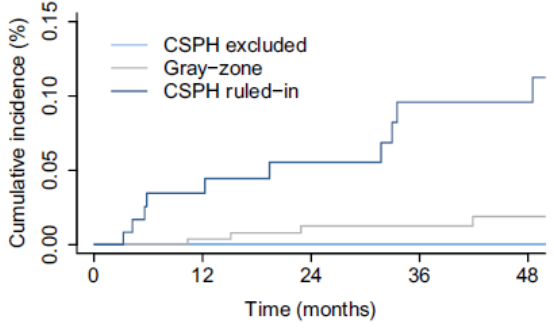
755 cACLD patients followed for a median of 38 months

Prevalence

42.5%	40.7%	16.8%

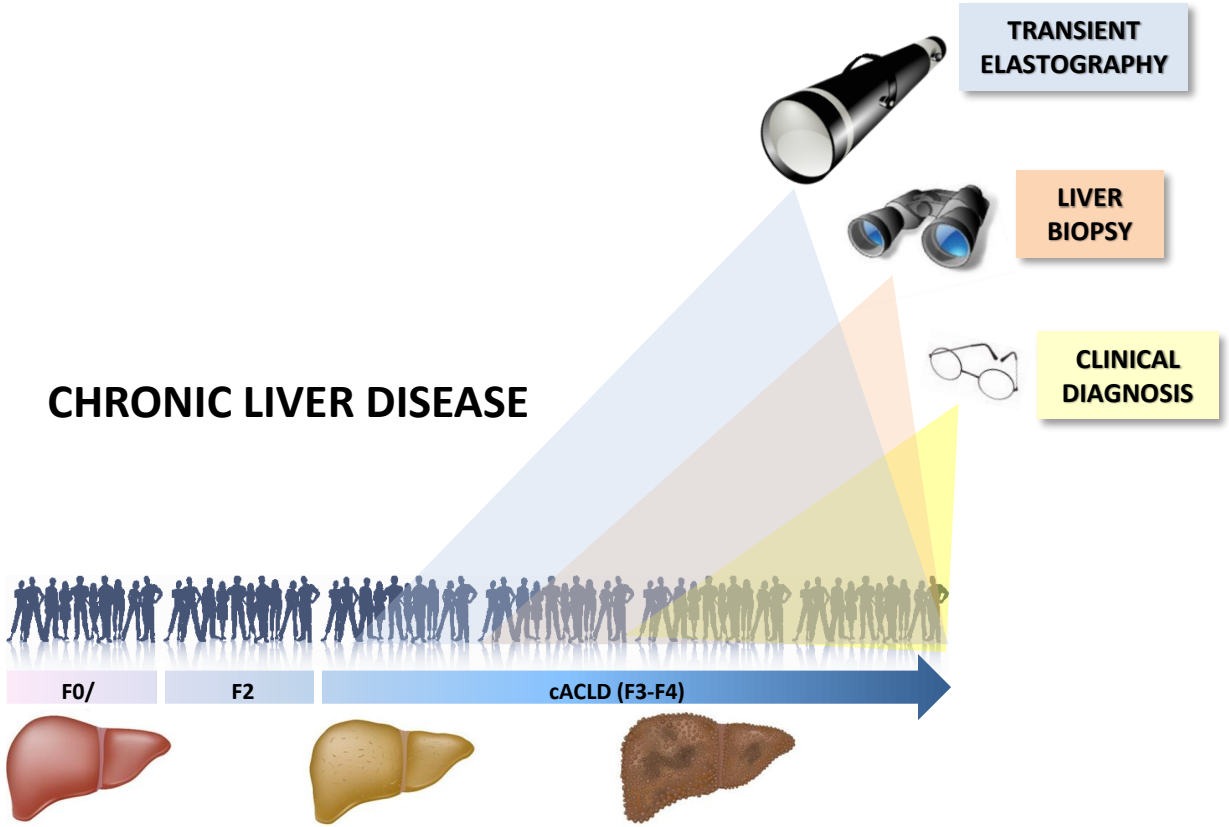
Cumulative incidence of hepatic decompensation at 3 years

0%	1.3%	9.6%



Semmler, et al. J Hepatol 2022

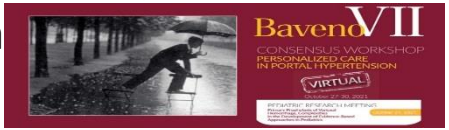
LSM-VARICES


TRANSIENT ELASTOGRAPHY
LIVER BIOPSY
CLINICAL DIAGNOSIS
CHRONIC LIVER DISEASE
F0/
F2
cACLD (F3-F4)

LSM-VARICES

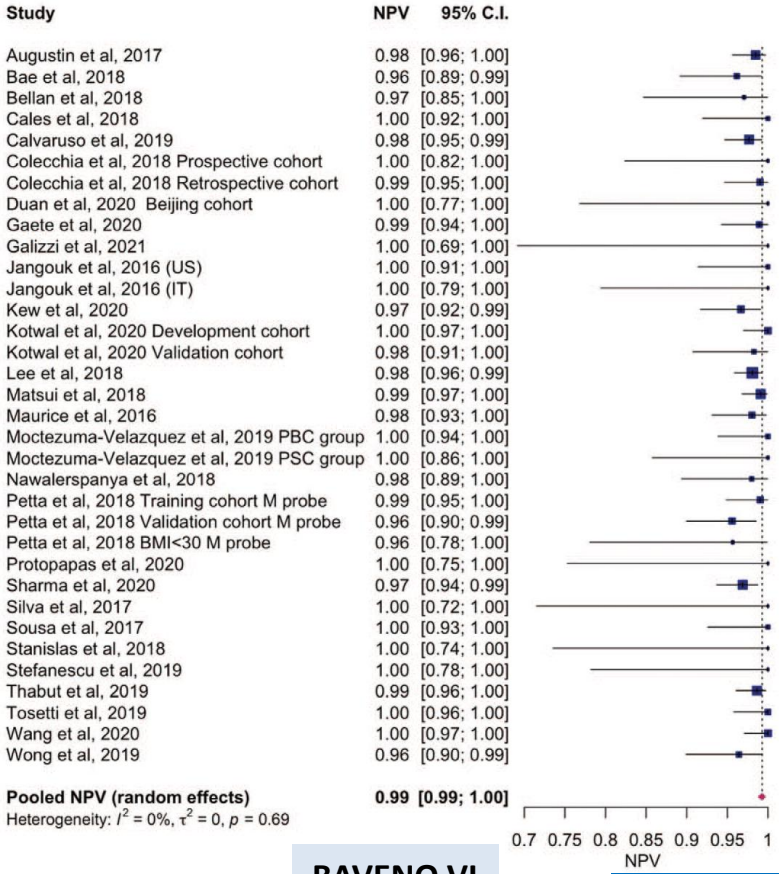
Patients with a liver stiffness <20 kPa and with a platelet count >150,000 have a very low risk (>5%) of having varices requiring treatment and can avoid screening endoscopy (25% saved). >25 validation studies.

The progressive change in approach to the management of compensated cirrhosis, progressively focusing on treating CSPH with NSBB independently of the presence of varices, might render these criteria less releva

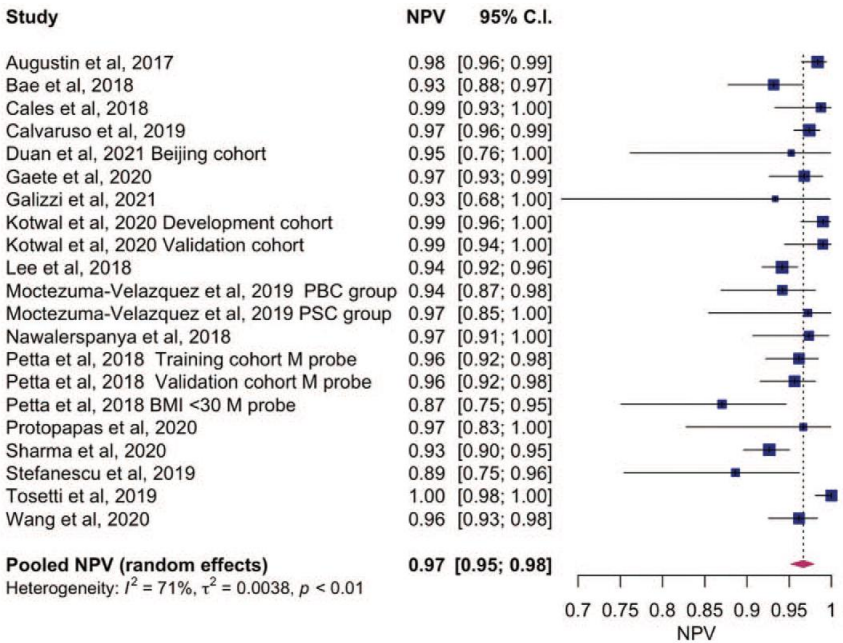


Patients with compensated cirrhosis not candidates for NSBB (contraind./intol.) for the prevention of decompensation should undergo an endoscopy for variceal bleeding screening if LSM by TE ≥20 kPa or platelet count ≤150x10^9L.

LSM-VARICES



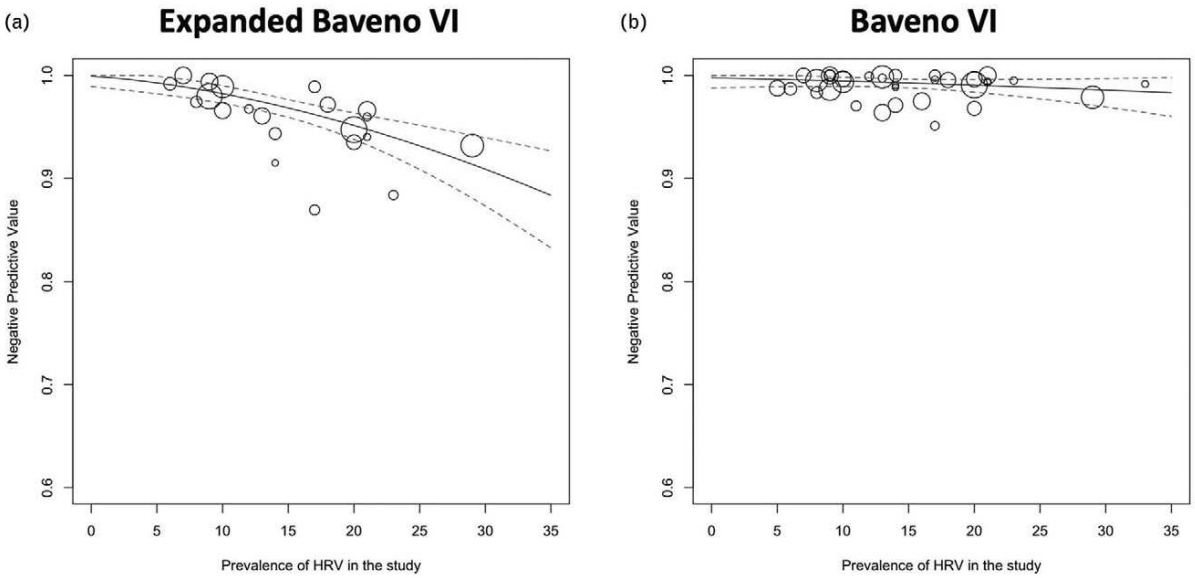
BAVENO VI



EXPANDED BAVENO VI

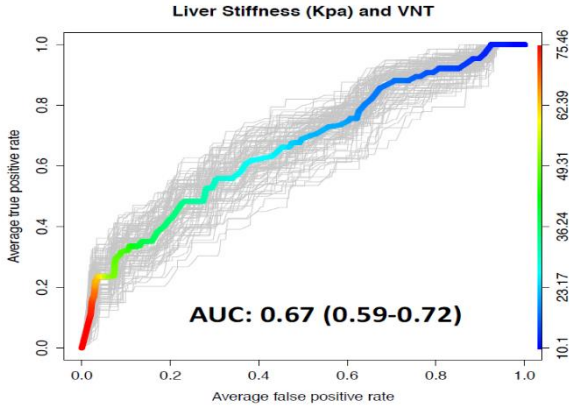
Bai, et al. Cu Op Gastro 2022

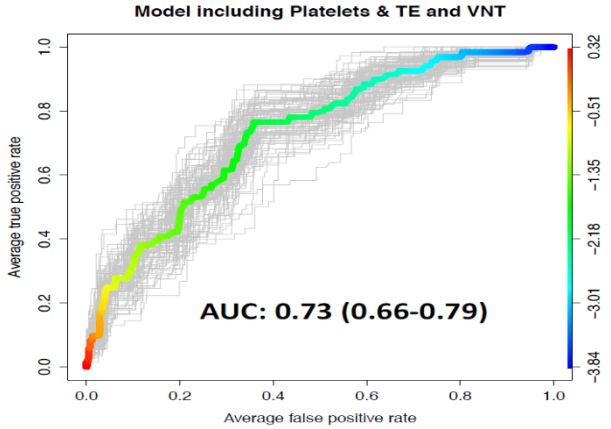
LSM-VARICES

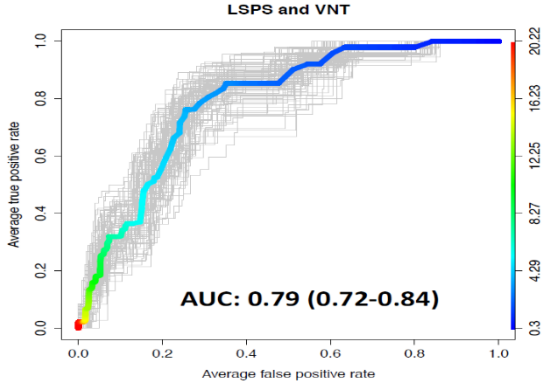


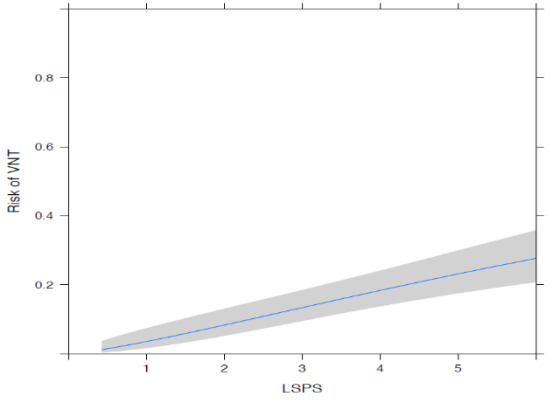
Bai, et al. Cu Op Gastro 2022

LSM-VARICES



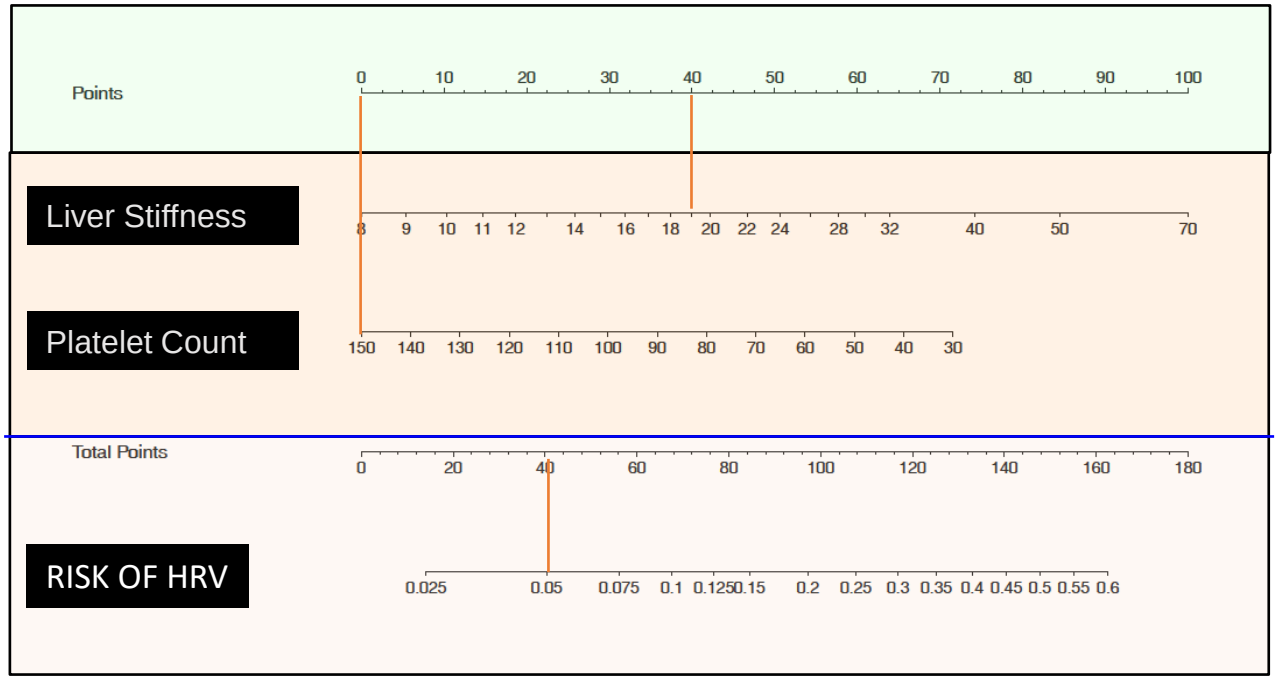






JG Abraldes, et al. Hepatology 2016

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%

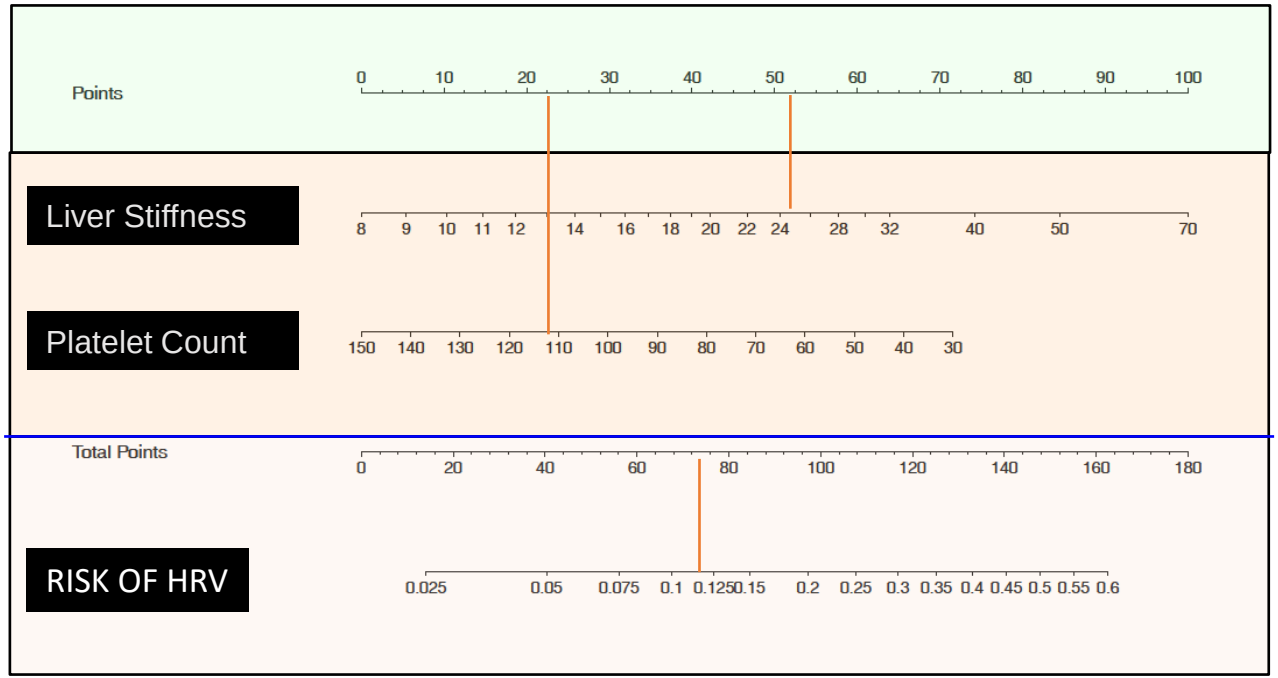
NEW CRITERIA-VALIDATION-ETIOLOGIES

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

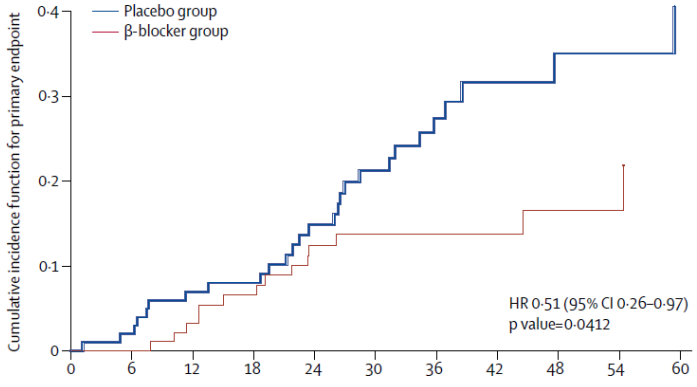
Risk of VNT
(Anticipate study, 2016, Hepatology)



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

CSPH-PREDESCI

A



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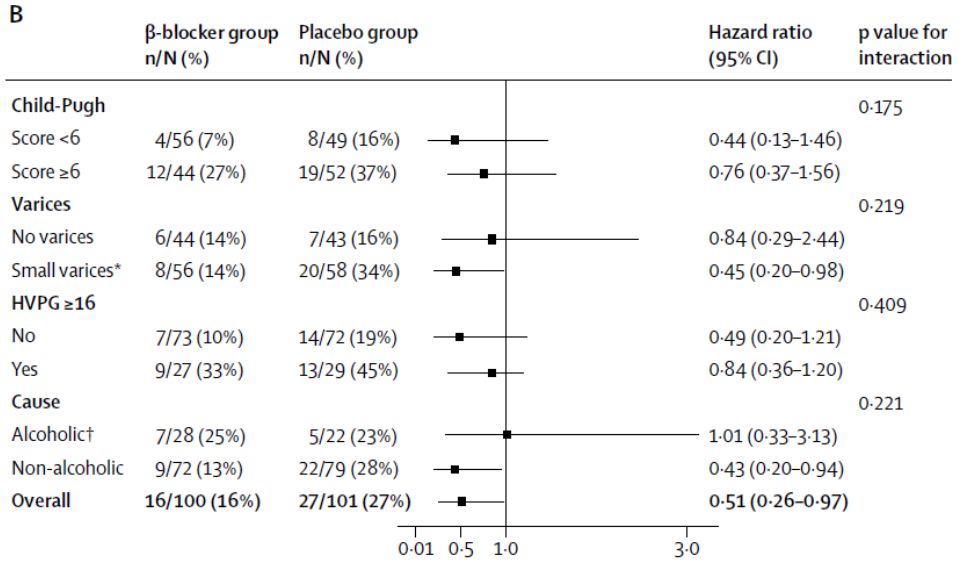
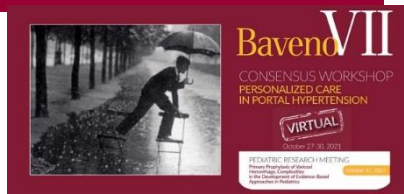
Placebo	101	99	94	86	72	59	42	26	19	13	6
Primary outcome (deaths)											
β blockers		1 (1)	3 (1)	4 (2)	5 (2)	1 (1)	0	0	1 (1)	0	1
Placebo		2 (2)	5 (1)	1	6 (2)	5 (1)	4 (3)	2 (1)	1 (1)	0	1
Censoring events											
β blockers		3	6	3	6	8	12	17	10	5	7
Placebo		0	0	7	8	8	13	14	6	6	6

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



CSPH-Non-invasive diagnosis-LSM

Liver decompensation & Liver-related death

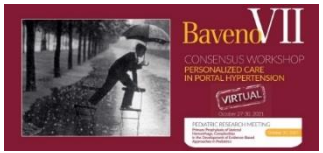
+Plat >150, Baveno VI-Avoid endoscopy

+Plat ≥150, Exclude CSPH

5 kPa → 10 kPa → 15 kPa → 20 kPa → 25 kPa

Normal

Exclude cACLD



Assume cACLD

Assume CSPH:
HCV, HBV, ALD
Nonobese NASH

CSPH-Non-invasive diagnosis-LSM

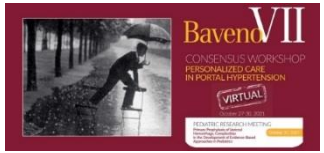
Table 2
Accuracy of LSM for the diagnosis of CSPH

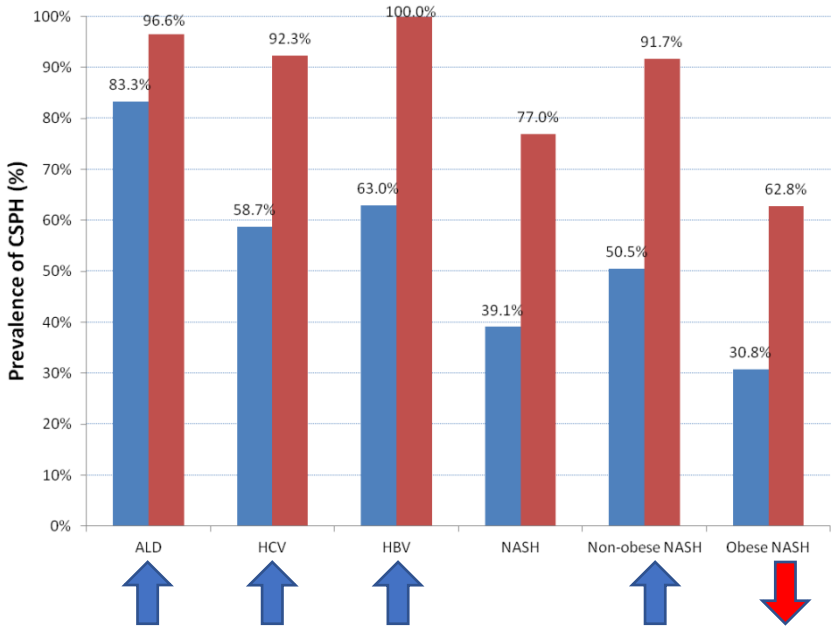
Study, Year	Study Design	Population	Correlation Coefficient Between LSM and HVPG	AUROC for CSPH	Cut-off for CSPH	Sensitivity (%)	Specificity (%)
TE (only studies with ≥100 patients selected)							
Bureau et al,[18] 2008	Prospective	144 patients with HCV or alcoholic cirrhosis	0.858	0.945	21 kPa	89.9	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

LSM-CSPH-RULING IN/OUT

Virus and/or alcohol related cACLD and non-obese (BMI <30 kg/m2) NASH cACLD, a LSM value by TE ≥25 kPa is sufficient to rule in CSPH





LSM≥25 kPa ruling in

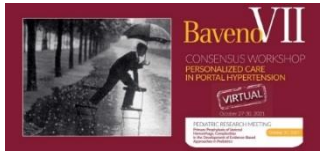
(>90% PPV, >90% Sp)

836 cACLD patients (virus/alcohol/NASH)

Pons, et al. AJG 2021

LSM-CSPH-RULING IN/OUT

LSM by TE ≤15 kPa plus platelet count ≥150x109/L rules out CSPH in cACLD patients



836 cACLD patients (virus/alcohol/NASH)

Pons, et al. AJG 2021

LSM-CSPH-RULING IN/OUT

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)

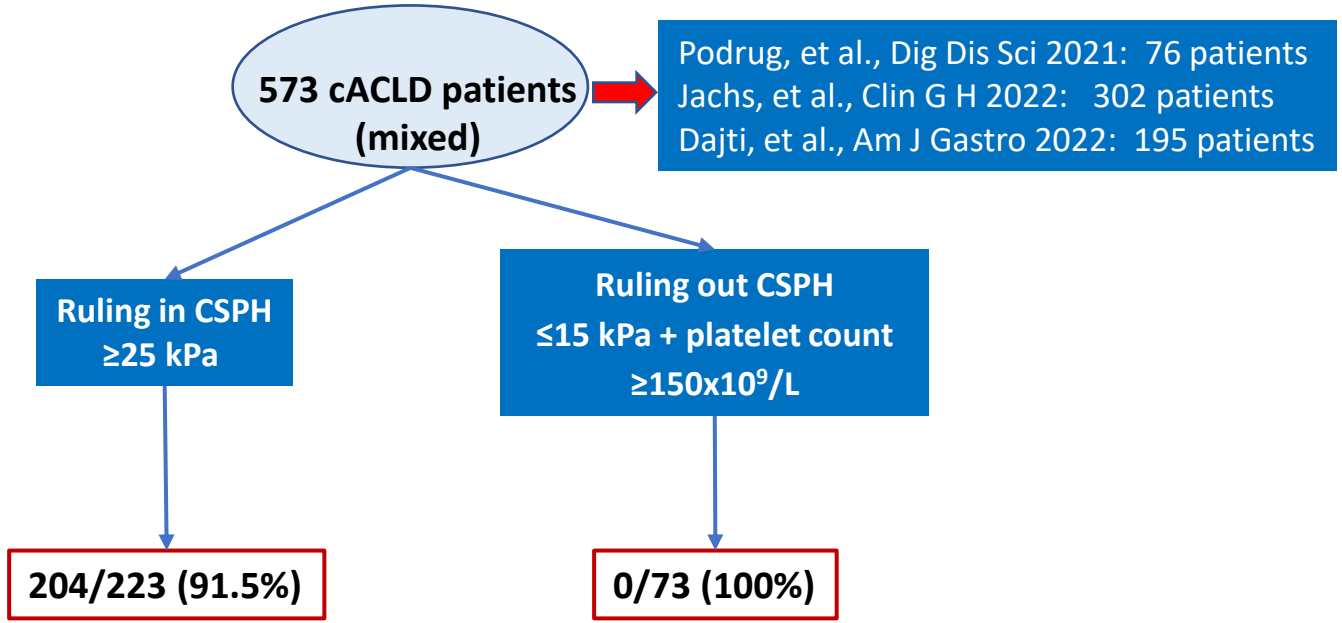
ALD, alcoholic liver disease; CI, confidence interval; HBV, chronic hepatitis B; HCV, chronic hepatitis C; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; NASH, nonalcoholic steatohepatitis.
[a]Number of patients within LSM cutoff.
[b]Number of patients without clinically significant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

S >90%

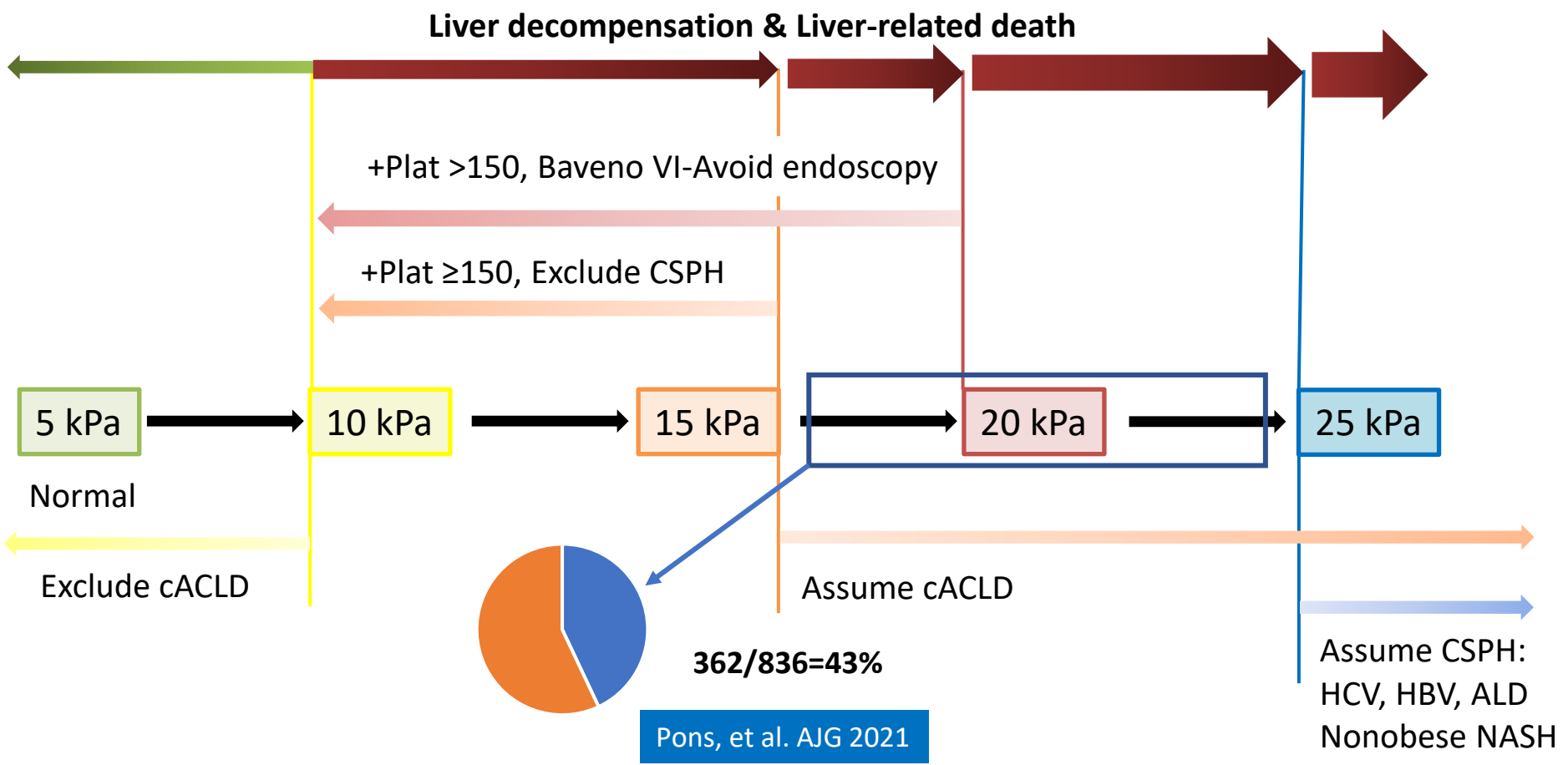
836 cACLD patients (virus/alcohol/NASH)

Pons, et al. AJG 2021

LSM-CSPH-RULING IN/OUT-VALIDATION

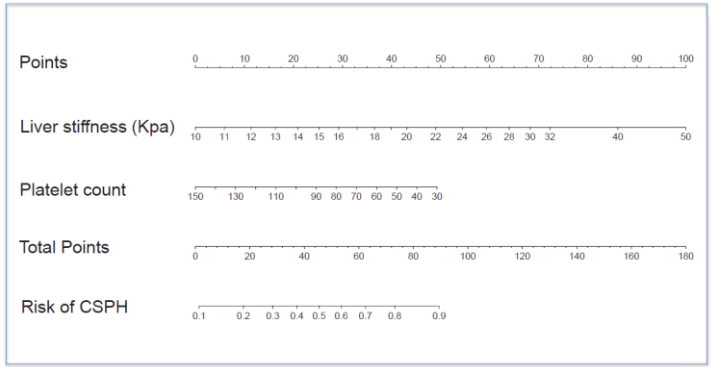


LSM-CSPH-GREY AREA



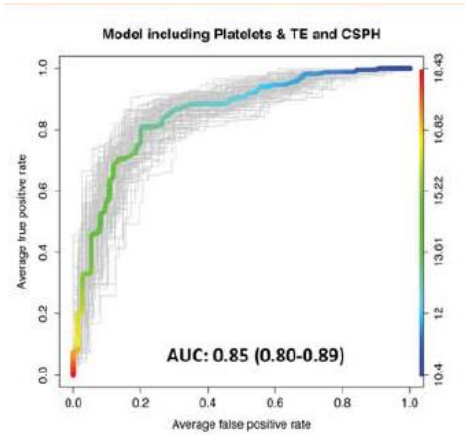
Pons, et al. AJG 2021

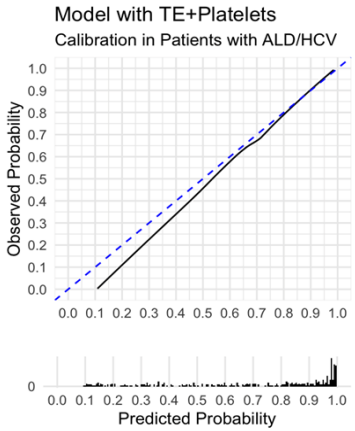
LSM-CSPH-GREY AREA-VIRUS/ARLD



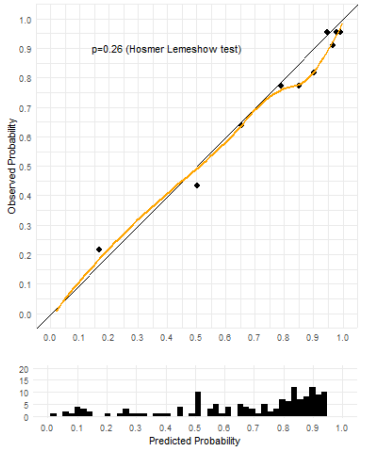
Risk prediction model for CSPH (virus/alcohol)

ANTICIPATE
Abraldes, et al. Hepatology 2016



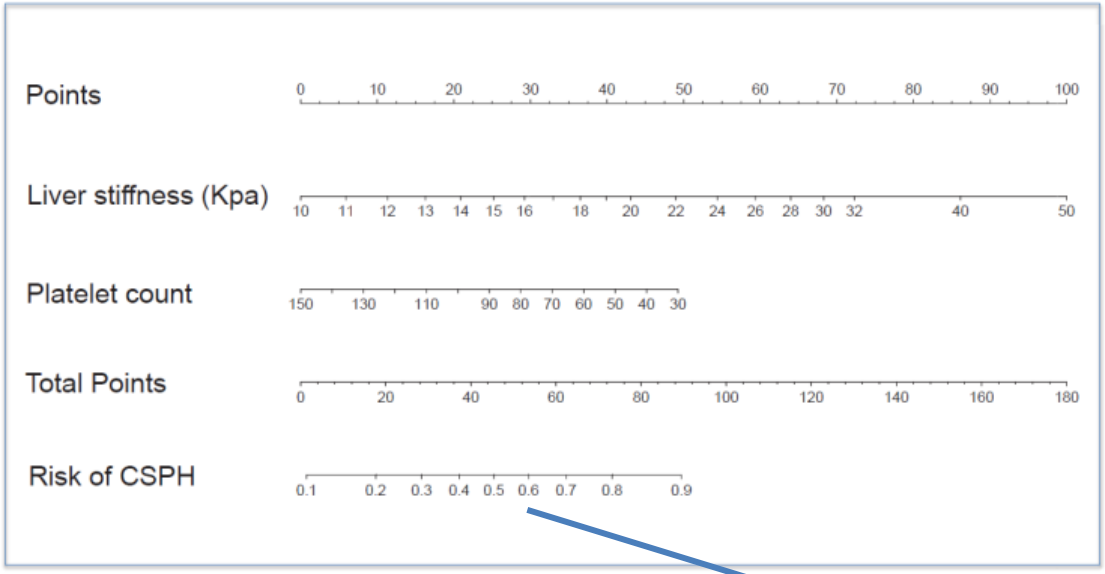


Pons, et al. AJG 2021



Rabiee, et al. Hep Comm 2022

LSM-CSPH-GREY AREA-VIRUS/ARLD



Risk prediction model for CSPH (virus/alcohol)

CSPH risk of at least 60%:

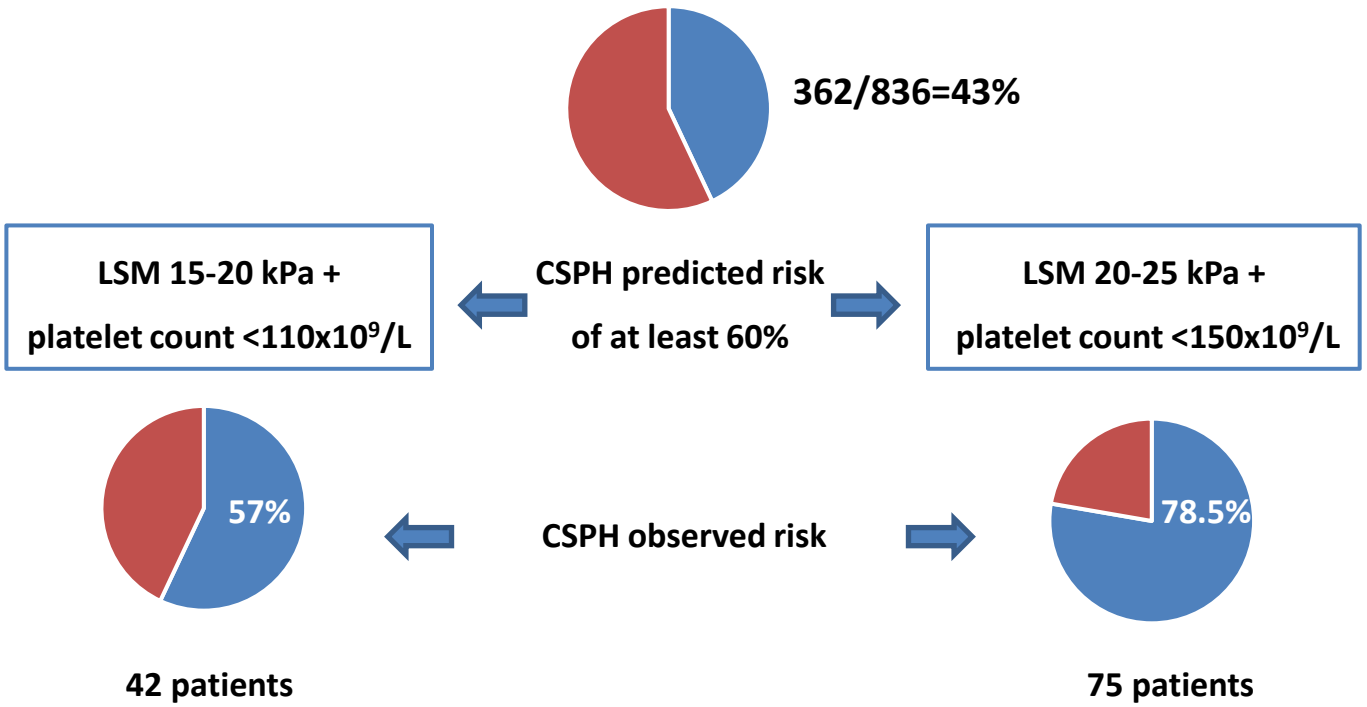
-LSM between 20-25 kPa and platelet count <150x10^9/L.

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

Pons, et al. AJG 2021

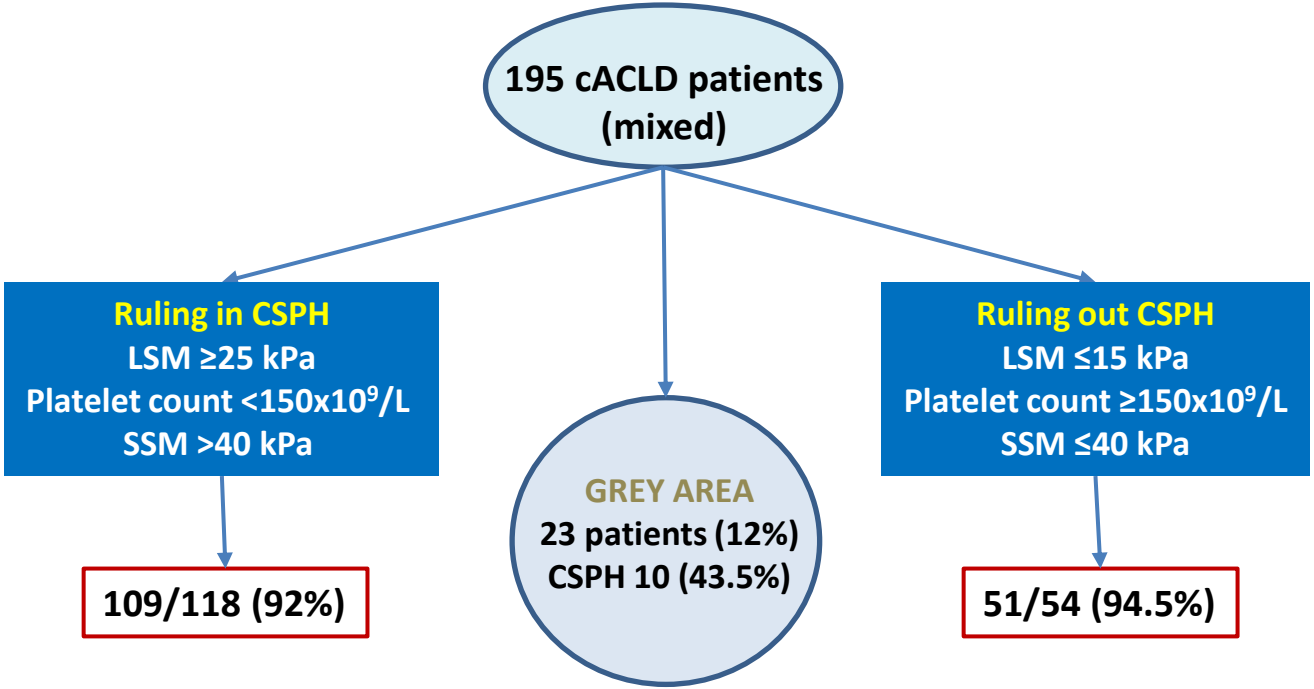
Abraldes, et al. Hepatology 2016

LSM-CSPH-GREY AREA



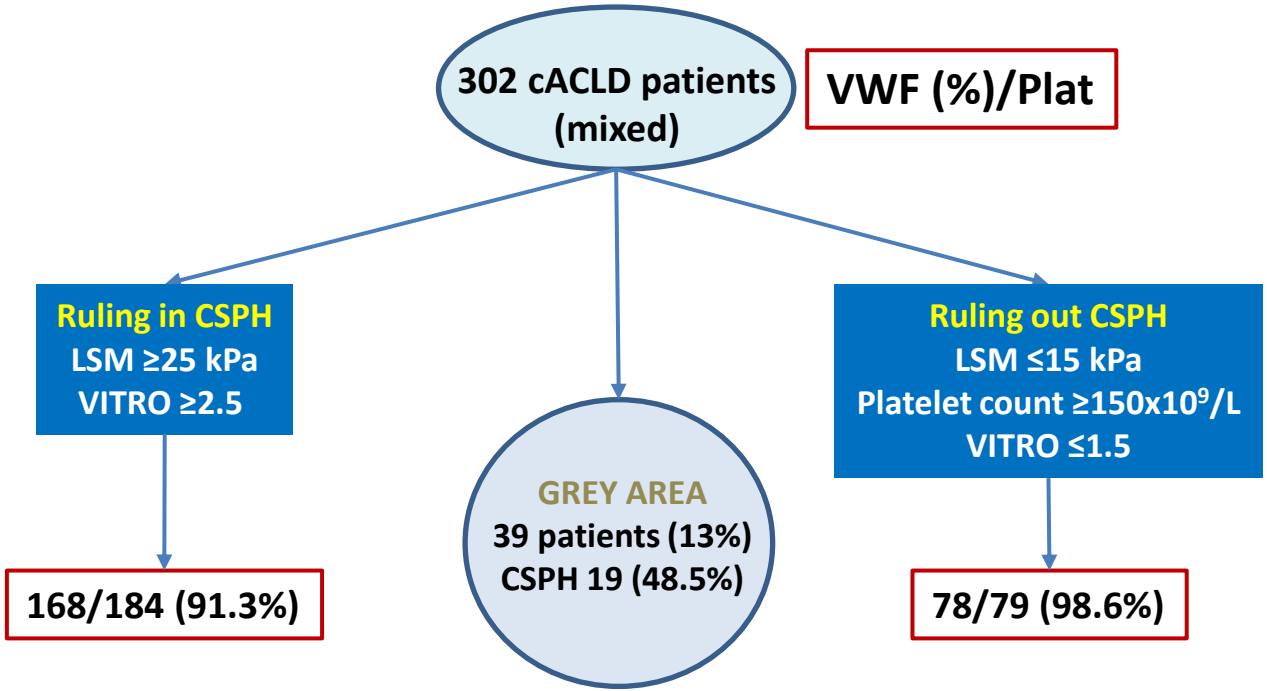
Pons, et al. AJG 2021

LSM-CSPH-GREY AREA-SSM (2 criteria)



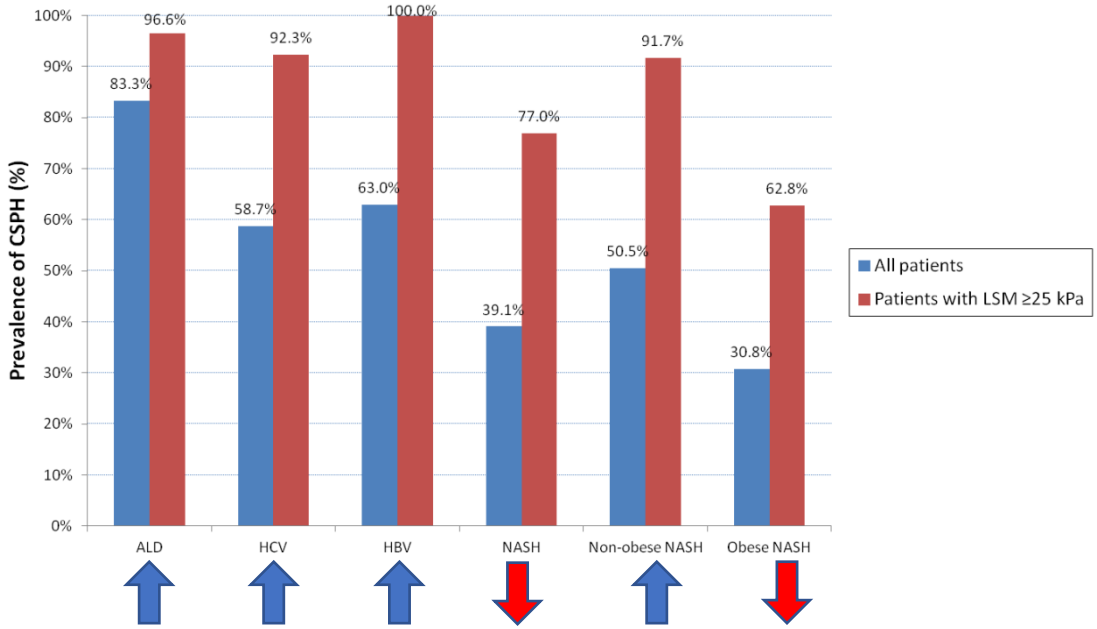
Dajti, et al., Am J Gastro 2022

LSM-CSPH-GREY AREA-VITRO-Sequential



Jachs, et al., Clin Gastro Hepatol 2022

LSM-CSPH-NASH



836 cACLD patients (virus/alcohol/NASH)

Pons, et al. AJG 2021

LSM-CSPH-NASH

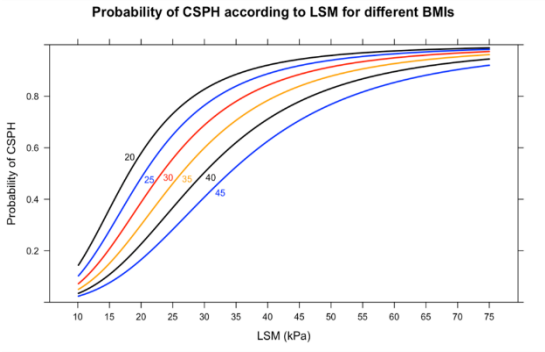
Pons, et al. AJG 2021
-248 NASH
-CSPH 39%
-Unselected cACLD

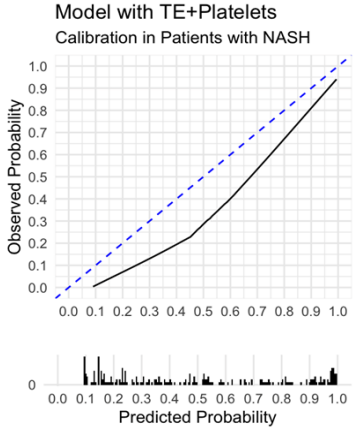
LSM ≥25 kPa: CSPH 77%

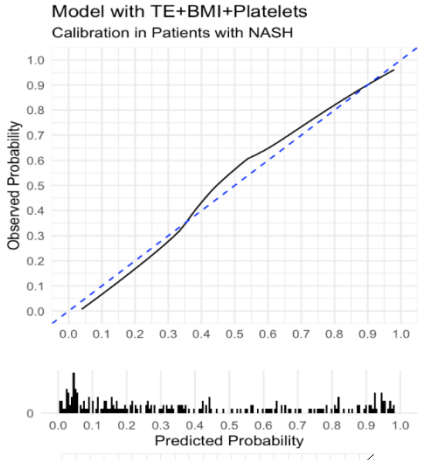
Rabiee, et al. Hep Comm 2022
-222 NASH
-CSPH 74%
-Emricasan study
-Selected for CSPH-HVPG >12 mmHg

LSM ≥25 kPa: CSPH 86%

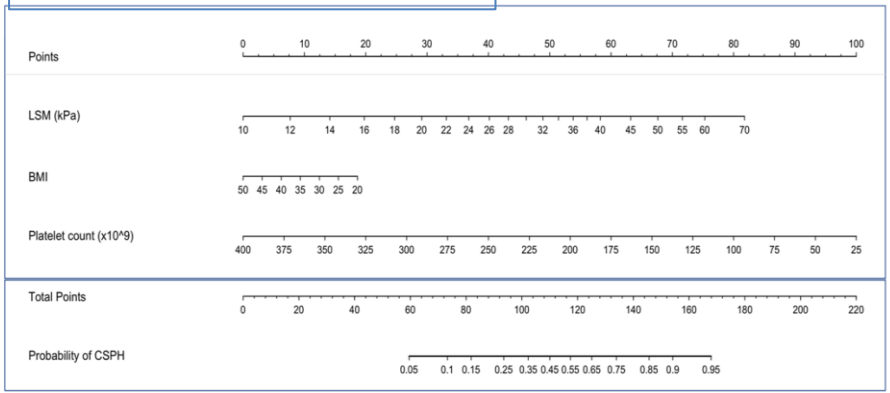
LSM-CSPH-NASH

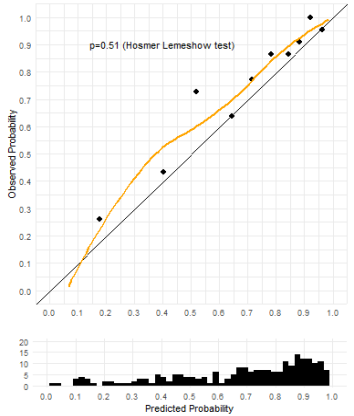






New ANTICIPATE-NASH model





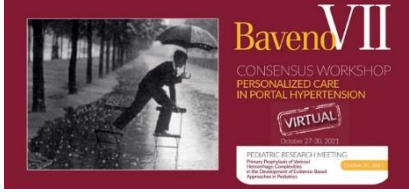
Pons, et al. AJG 2021

Rabiee, et al. Hep Com 2022

LSM-CSPH-NASH

LSM (kPa)	BMI range (kg/m^2)	Platelet count ($x10^9/L$)
15	20	80
	25	75
	30	60
	35	45
20	20	135
	25	120
	30	100
	35	90
25	20	160
	25	150
	30	140
	35	125
30	20	190
	25	180
	30	165
	35	155

Maximum platelet count needed for different combinations of liver stiffness measurement (LSM) and body mass index values to obtain a clinically significant portal hypertension risk prediction of 60% in patients with non-alcoholic steatohepatitis (NASH) using the risk prediction of the ANTICIPATE-NASH model.



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

Clinically significant portal hypertension (CSPH)

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

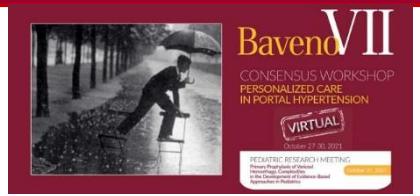
-CSPH: <25 kPa ANTICIPATE model for viral/alcohol (CSPH risk of at least 60%):

-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.

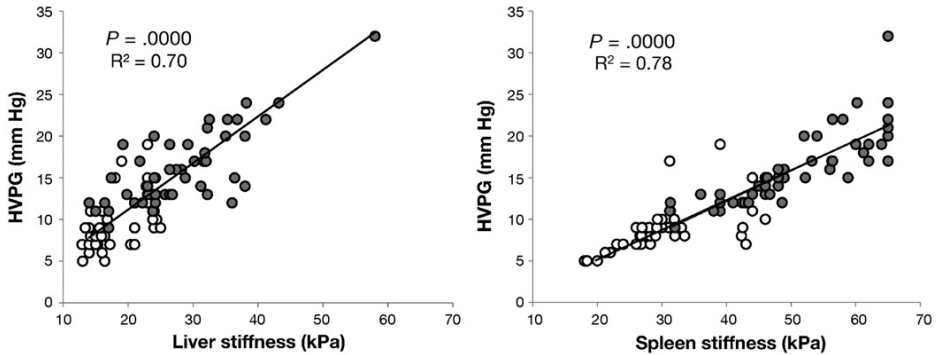
-Ruling out CSPH: ≤15 kPa + pla ≥150 (>90% NPV, >90% Se).



SPLEEN STIFFNESS MEASUREMENT-SSM

SSM by TE can be used in cACLD due to viral hepatitis to rule out and rule in CSPH (SSM <21 kPa and SSM >50 kPa, respectively).

Not candidates for NSBBs out of Baveno VI criteria (LSM by TE ≥ 20 kPa or platelet count ≤150x109L), SSM ≤40 kPa by TE can be used to identify those at low probability of HRV, avoiding endoscopy.



Colecchia, et al. Gastro 2012

-Mostly viral etiology

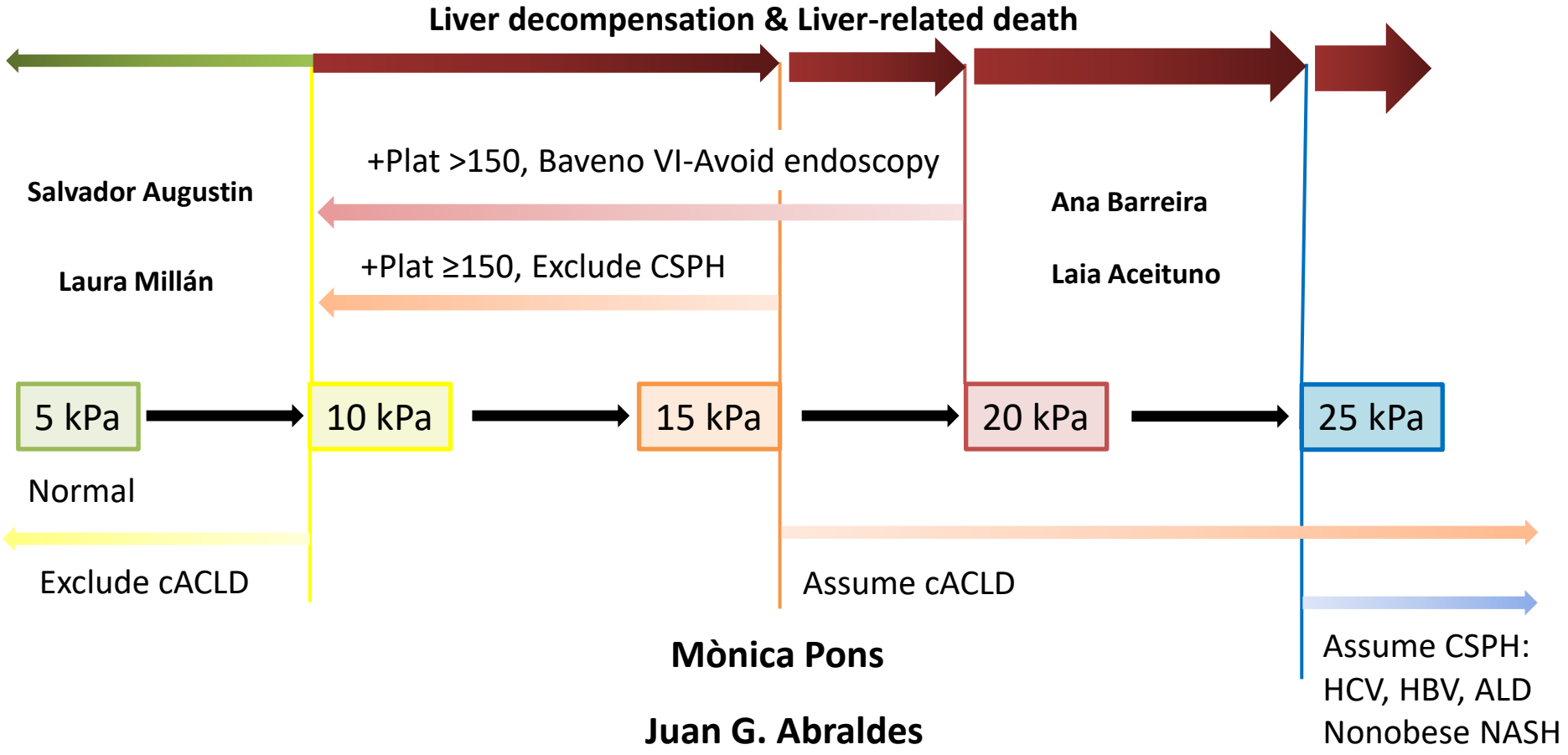
-TE 50 to 100 Hz (evidence)

-Technical: failures (20% to 5%)

-Logistic: time, dedication

-Added value to LSM?: Varices/**CSPH**/**LRE**

-SSM alone/combination (sequential) to LSM?



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

THANK YOU

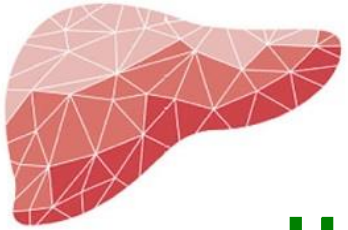
Vall d'Hebron

Liver Unit

Vall d'Hebron Research

Liver Diseases Group

THANK YOU



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