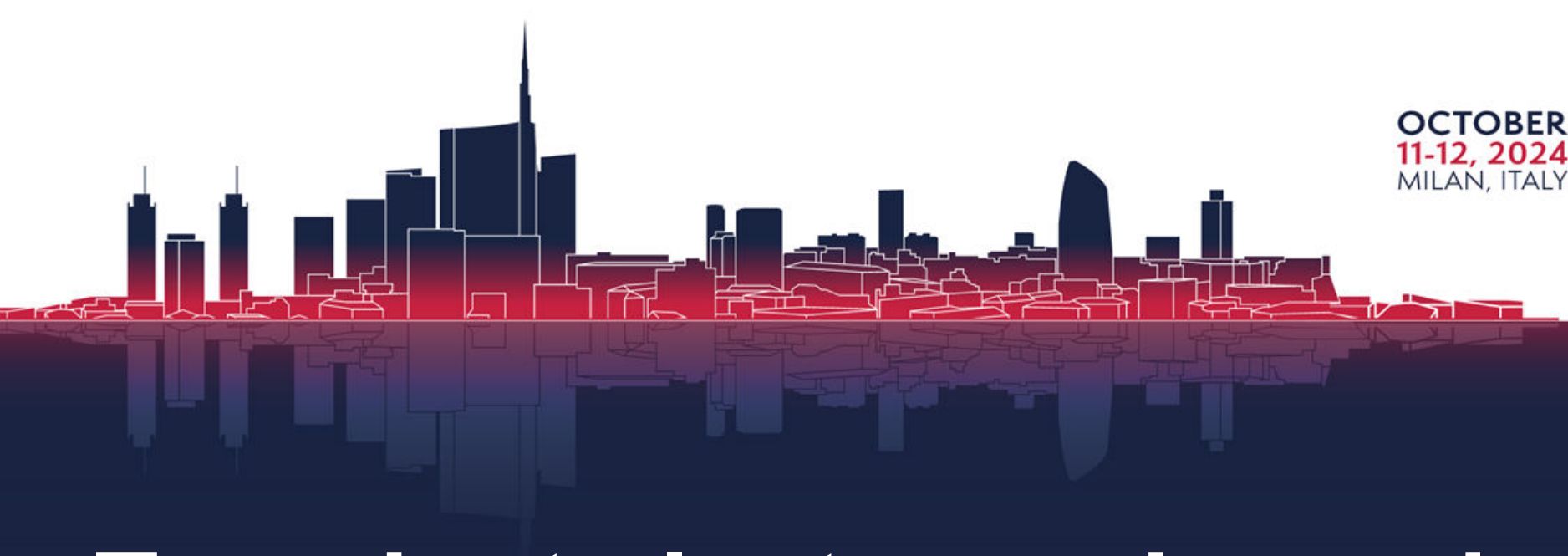


OCTOBER 11-12, 2024 MILAN, ITALY

DeltaCure 3rd International Meeting

Transient elastography and other non-invasive tests in hepatitis delta

Dr. med. Lisa Sandmann

Department of Gastroenterology, Hepatology, Infectious Diseases and Endocrinology

Hannover Medical School

Disclosure of potential conflicts of interest

Consultation:	Roche, Gilead
Honoraria:	Roche, Gilead, Abbvie
Travel support	Abbvie, Gilead

Why do we need non-invasive tests in hepatitis delta?

Why do we need non-invasive tests in ~~hepatitis delta~~?
chronic liver disease?

Why do we need non-invasive tests in ~~hepatitis delta~~ chronic liver disease?

absent / mild

cirrhosis / liver-related events

Severity of liver disease

Risk of disease progression

Treatment indication

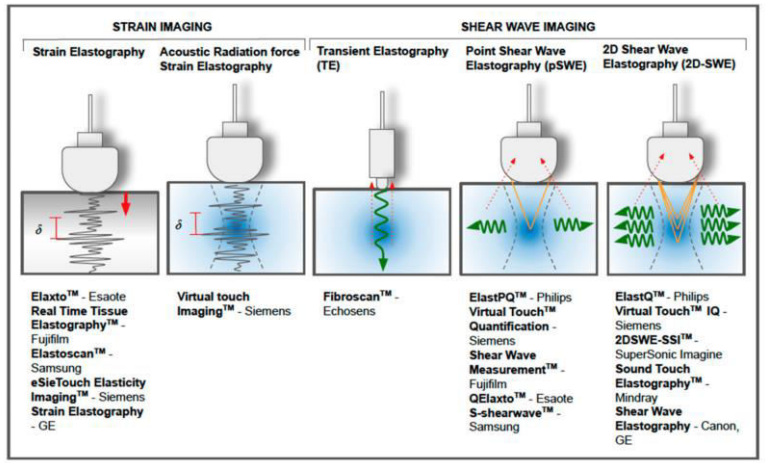
Clinical monitoring

Advantages of non-invasive tests

Fibrosis scores:
i.a. FIB-4, APRI, AAR, DFS[1], D4FS[2]

Imaging: Ultrasound

Liver stiffness measurement:
i.a. Transient elastography (TE)
Shear wave elastography (SWE)
Acoustic Radiation Force Impulse elastography (ARFI)



1) Lutterkort et al., Liver Int 2017
2) Da BL, et al. Antivir Res 2020
Cé, M et al. *BioMedInformatics* **2023**, 3(1), 17-43

Advantages of non-invasive tests

No / little risk (venous puncture)

Availability

Time

(easy) longitudinal monitoring

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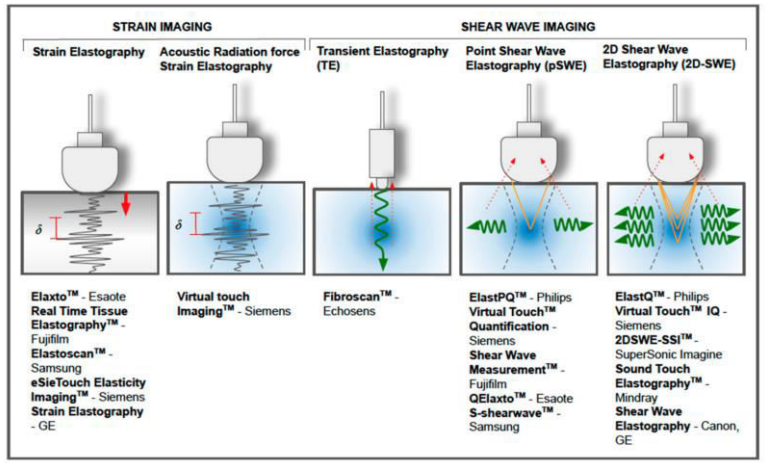

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Advantages and disadvantages of non-invasive tests

No / little risk (venous puncture)

Availability

Time

(easy) longitudinal monitoring

No histology = no additional information

Overestimation of fibrosis due to hepatic inflammation

Limited validation in CHD?

What does the guideline recommend?

When should invasive (liver biopsy) and non-invasive tests (NITs) be used in the clinical management of patients with hepatitis D?

Statement

- Fully published data on the use of NITs in patients with CHD are currently limited and the correlation with liver histology is missing in a significant proportion of cases **(LoE 4, strong consensus).**

Recommendations

- Liver biopsy is recommended whenever it may contribute to the patient's management or for grading and staging liver disease when clinical signs or indirect evidence (by imaging techniques) of cirrhosis are absent **(LoE 3; strong recommendation, consensus).**
- NITs may be used to assess advanced liver disease, but specific cut-off values are not well established **(LoE 5, weak recommendation, strong consensus).**

EASL Clinical Practice Guidelines 2023, J Hepatol. 2023

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Received: 3 November 2023 | First decision: 27 November 2023 | Accepted: 2 January 2024
DOI: 10.1111/apt.17878
APT Alimentary Pharmacology & Therapeutics WILEY

Liver stiffness measurement as a noninvasive method for the diagnosis of liver cirrhosis in patients with chronic hepatitis D virus infection

Lisa Sandmann[1,2] | Elisabetta Degasperi[2,3,4] | Kerstin Port[1] | Soo Aleman[2,5,6] | Jeffrey J. Wallin[7] | Dmitry Manuilov[7] | Ben L. Da[7] | Markus Cornberg[1,2,8,9] | Pietro Lampertico[2,3,4] | Benjamin Maasoumy[1,8] | Heiner Wedemeyer[1,2,8,10] | Katja Deterding[1,10]

aga American Gastroenterological Association
Clinical Gastroenterology and Hepatology
Available online 30 August 2024

High Diagnostic Value of Transient Elastography for Advanced Fibrosis and Cirrhosis in Patients With Chronic Hepatitis Delta

Dominique Roulot,[1] Ségolène Brichler,[2] Richard Layese,[3] Louis D'alteroche,[4] Nathalie Ganne-Carrie,[5] Christiane Stern,[6] Antonio Saviano,[7] Vincent Leroy,[8] Françoise Roudot-Thoraval,[3] Victor De Ledinghen,[9] and the DELTAVIR study group

EASL Clinical Practice Guidelines 2023, J Hepatol. 2023
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n=276

aga American Gastroenterological Association
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n=230

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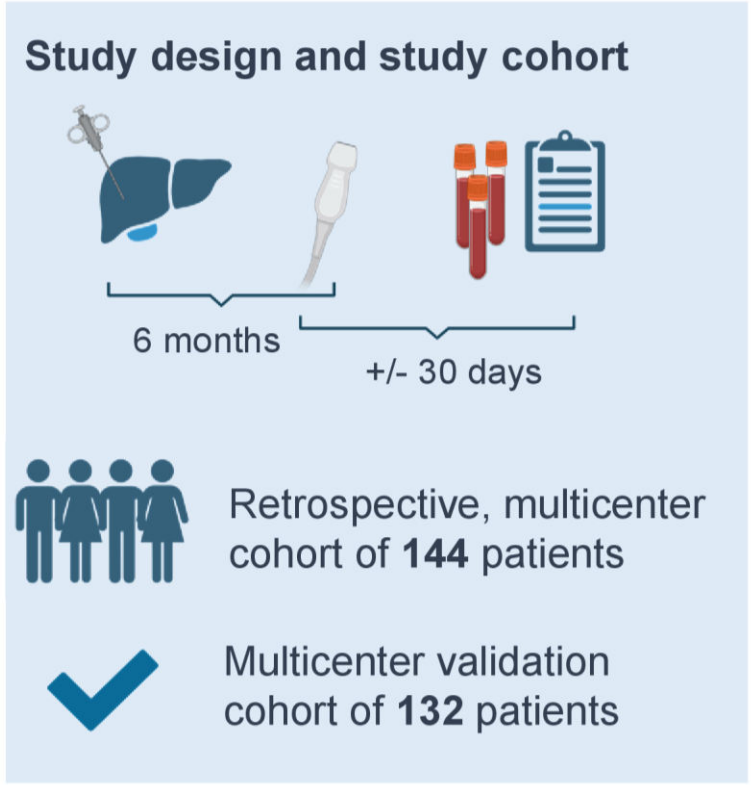
EASL Clinical Practice Guidelines 2023, J Hepatol. 2023
Sandmann L, et al, Aliment Pharmacol Ther 2024
Roulot D, et al, Clin Gastroenterol Hepatol 2024

Non-invasive assessment of disease severity

Liver stiffness measurement (Fibroscan®)

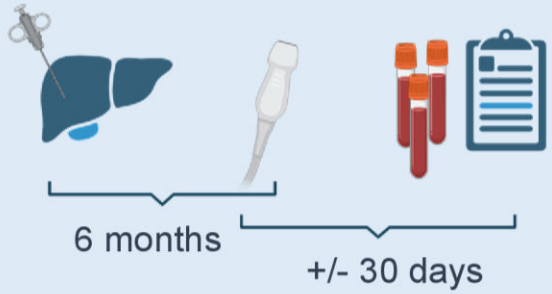


Sandmann L, et al. Aliment Pharmacol Ther. 2024

TE differentiates between fibrosis stages

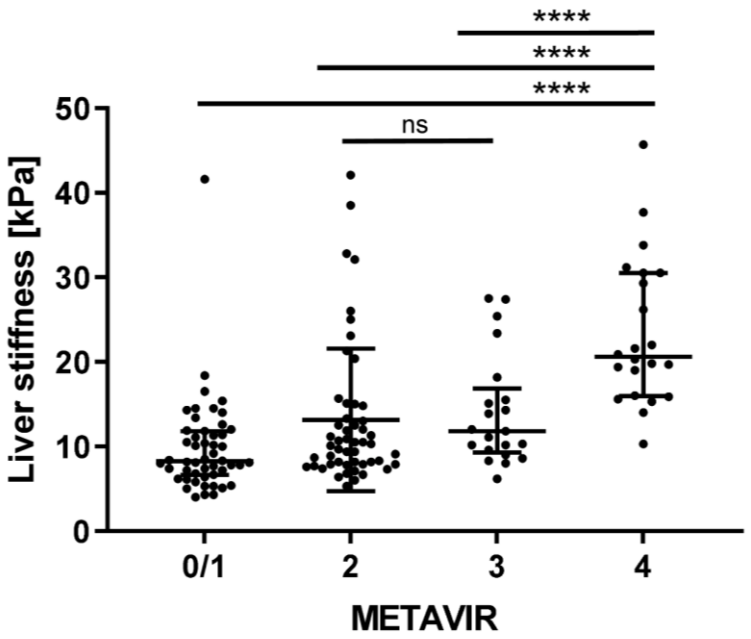
Liver stiffness measurement (Fibroscan®)

Study design and study cohort



Retrospective, multicenter cohort of **144** patients

Multicenter validation cohort of **132** patients



Sandmann L, et al. Aliment Pharmacol Ther. 2024

TE is the best NIT to differentiate cirrhosis from non-cirrhosis

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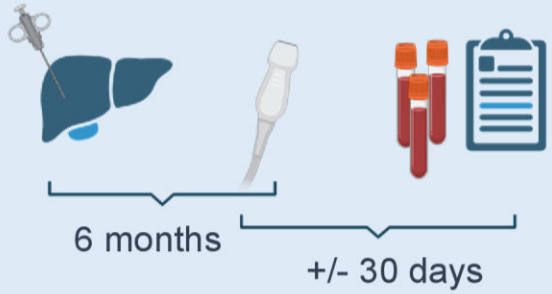

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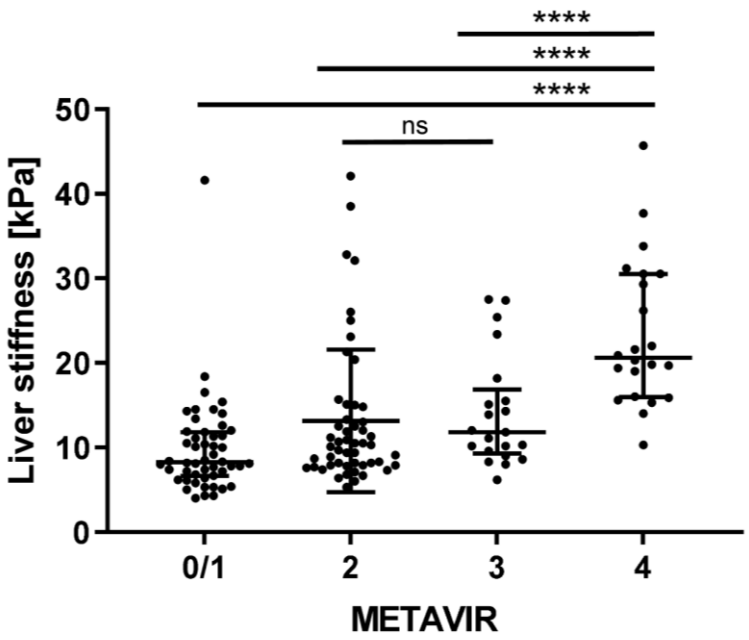

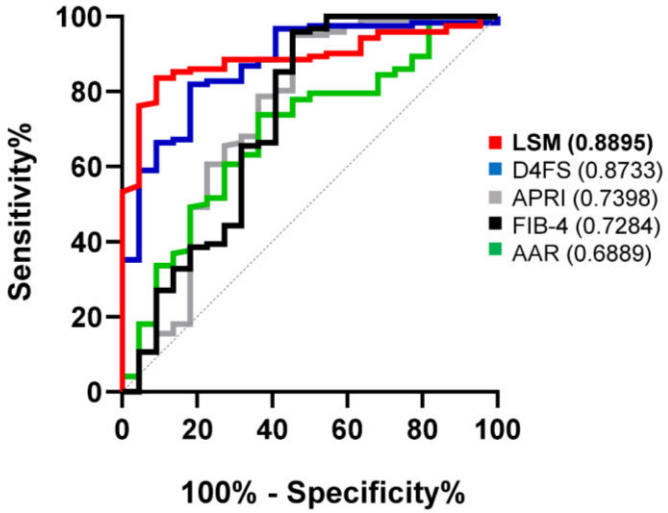

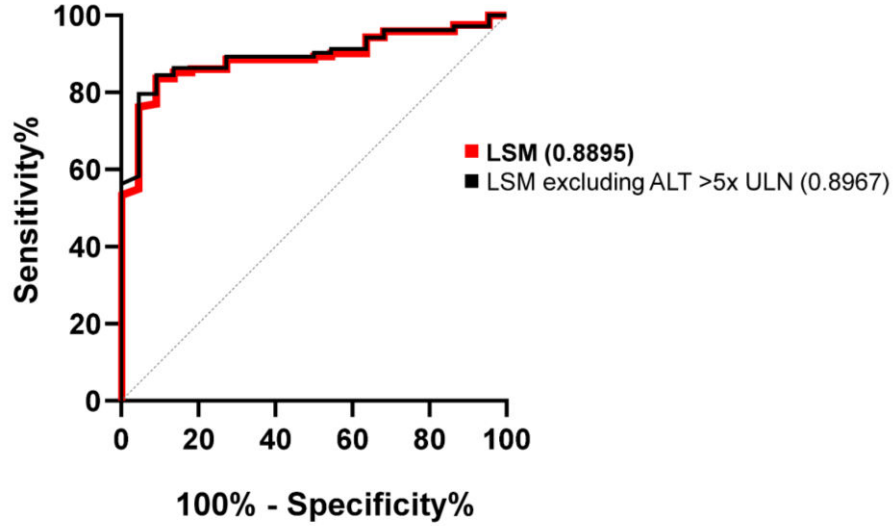

Gastroenterology Hepatology Infectious Diseases Endocrinology

D-SOLVE

DZIF Deutsches Zentrum für Infektionsforschung

Sandmann L, et al. Aliment Pharmacol Ther. 2024

Hannover Medical School

TE identifies patients without advanced chronic liver disease

Delta Cure 3rd International Meeting

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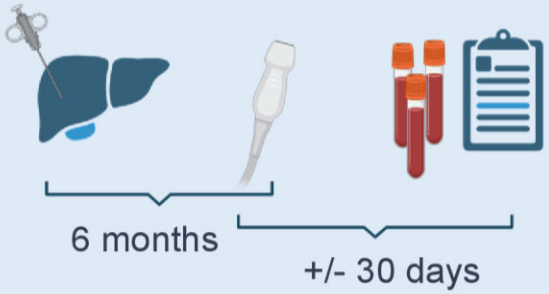

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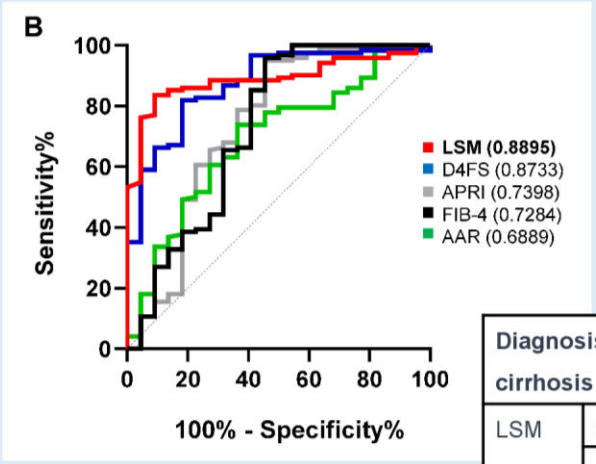
Key findings



- LSM is a **useful tool** for identifying patients at risk for liver cirrhosis and is **superior** to other NITs
- LSM is **better at ruling out cirrhosis** than it is at confirming cirrhosis
- The cut-offs of <**10.2 kPa** and <15.2 kPa reliably **diagnose non-advanced liver fibrosis and exclude cirrhosis** in the majority of patients

Diagnosis of cirrhosis		METAVIR 4 (n=22)	METAVIR ≤3 (n=122)	Se (%)	Sp (%)	PPV (%)	NPV (%)	Correctly classified
LSM	≥ 15.2 kPa	20	20	91	84	50	**98**	122 (85%)
	< 15.2 kPa	2	102					
Diagnosis of non-advanced fibrosis		METAVIR ≤2 (n=101)	METAVIR ≥3 (n=43)	Se (%)	Sp (%)	PPV (%)	NPV (%)	Correctly classified
LSM	< 10.2 kPa	56	6	55	86	**90**	45	93 (65%)
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Sandmann L, et al. Aliment Pharmacol Ther. 2024

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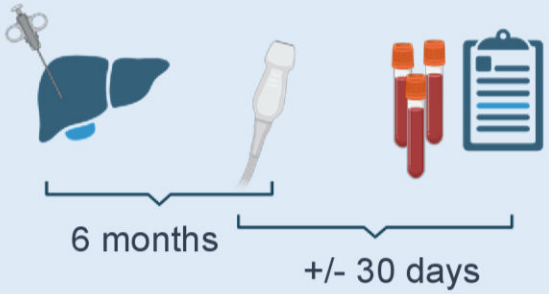

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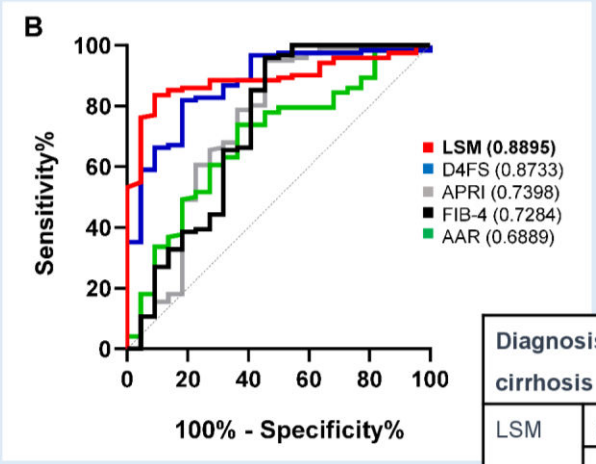

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- Fibroscan <15 kPa: Exclusion of liver cirrhosis (<F4)
- Fibroscan <10 kPa: Diagnosis of non-advanced liver disease (F0-2)

Sandmann L, et al. Aliment Pharmacol Ther. 2024

Transient elastography in the French real-life cohort

- Retrospective, multicenter French real-life cohort
- 230 patients with TE and liver biopsy within 6 months

Roulot D, et al. (DELTAVIR study group) Clin Gastroenterol Hepatol. 2024

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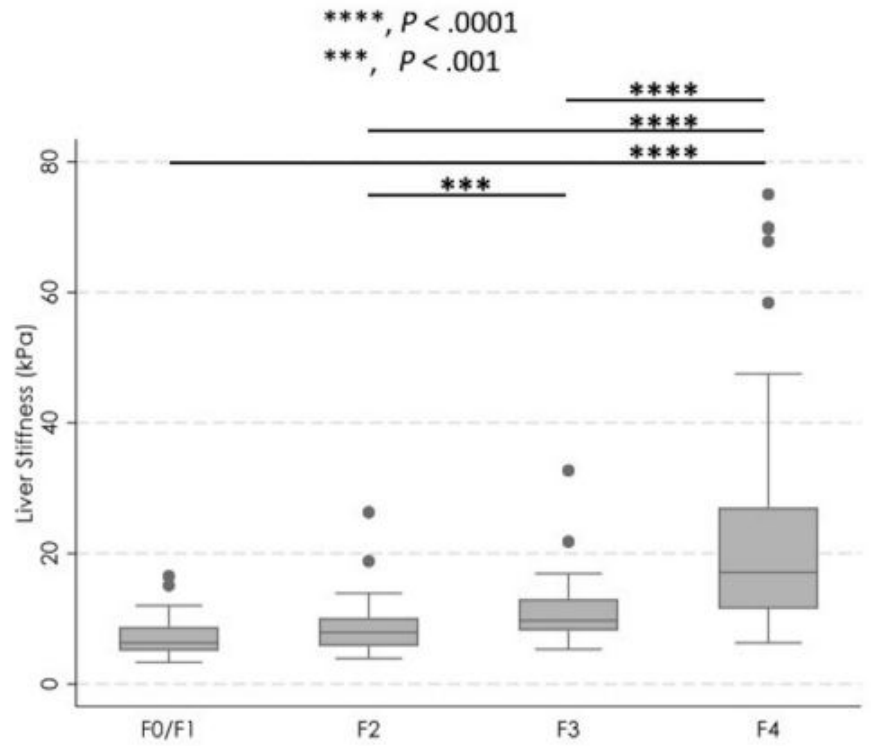

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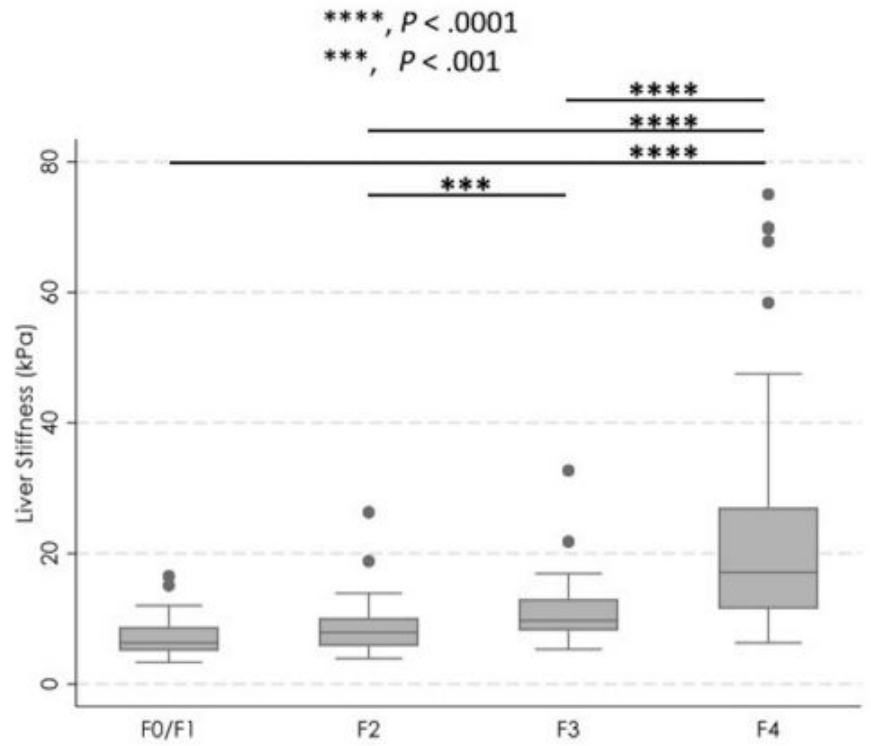
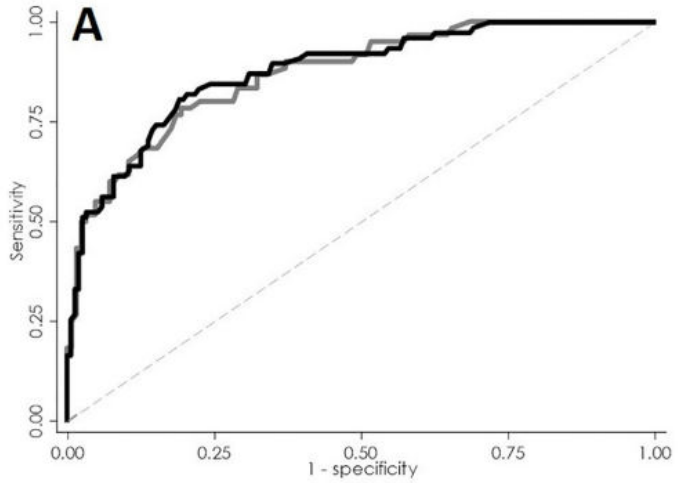
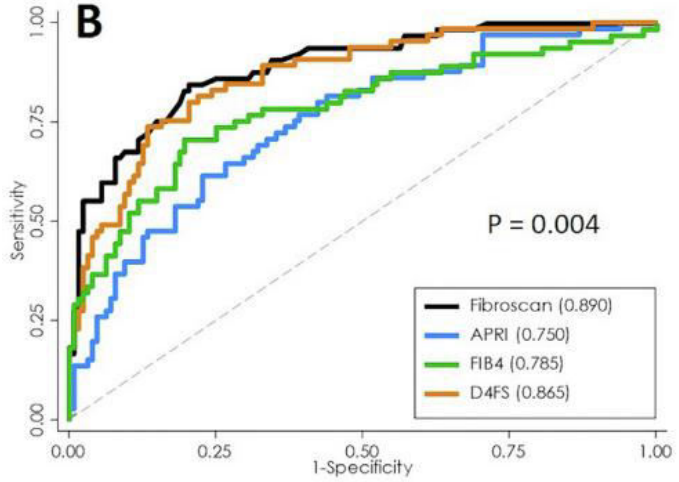




AUROC = 0.877 (95% CI: 0.831; 0.924)

With ALT < 5 ULN (in grey), AUROC = 0.870 (95% CI: 0.816; 0.924)



Roulot D, et al. (DELTAVIR study group) Clin Gastroenterol Hepatol. 2024

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Cirrhosis (F4)						
Fibroscan	**> 12.0**	**70.5**	**86.2**	**72.4**	**85.1**	**80.9**
APRI	≥ 1.25	63.1	77.7	58.6	80.8	72.8
FIB-4	≥ 2.07	70.1	81.1	65.3	84.3	77.4
D4FS	≥ 0.65	73.8	86.7	73.8	86.7	69.1
Advanced fibrosis (F3)						
Fibroscan	**≥ 10.4**	**70.2**	**83.5**	**82.5**	**71.7**	**76.5**
APRI	≥ 0.874	74.,	60.6	67.0	68.7	67.7
FIB-4	≥ 1.409	78.6	60.4	68.1	72.5	69.9
Significant fibrosis (F2)						
Fibroscan	**≥ 8.0**	**74.9**	**72.3**	**91.3**	**42.5**	**74.4**
APRI	≥ 0.771	74.7	68.3	89.8	41.8	73.3
FIB-4	≥ 1.16	76.9	60.5	87.6	41.9	73.4

Roulot D, et al. (DELTAVIR study group) Clin Gastroenterol Hepatol. 2024

TE identifies patients without advanced chronic liver disease

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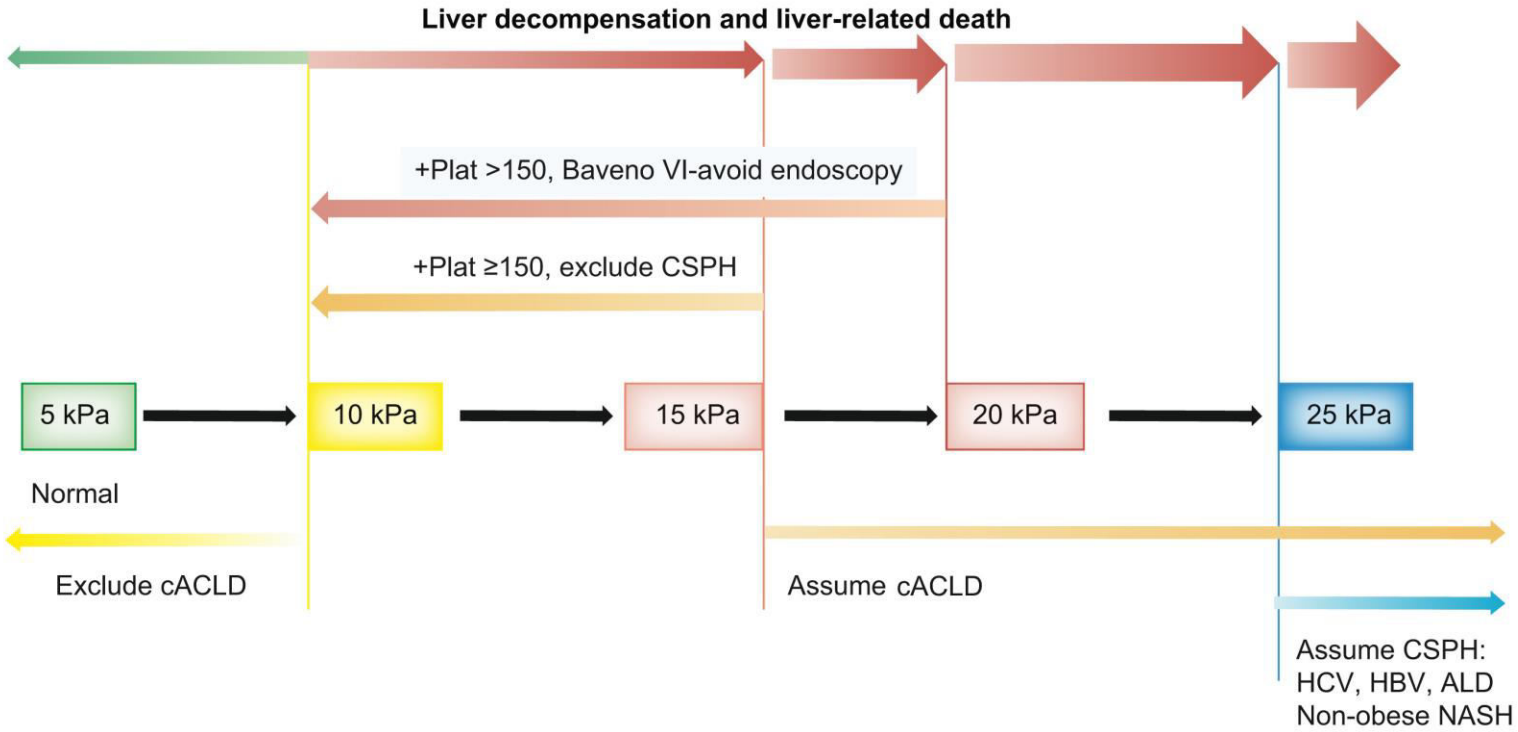
- Fibroscan ≤6 kPa: Exclusion of 89% of F2/F3/F4
- Fibroscan >10 kPa: Exclusion of 83.5% of non F3/F4

Roulot D, et al. (DELTAVIR study group) Clin Gastroenterol Hepatol. 2024

Diagnosis of compensated advanced chronic liver disease

„Rule of five“



Roberto de Franchis et al (Baveno VII faculty), J Hepatol 2022

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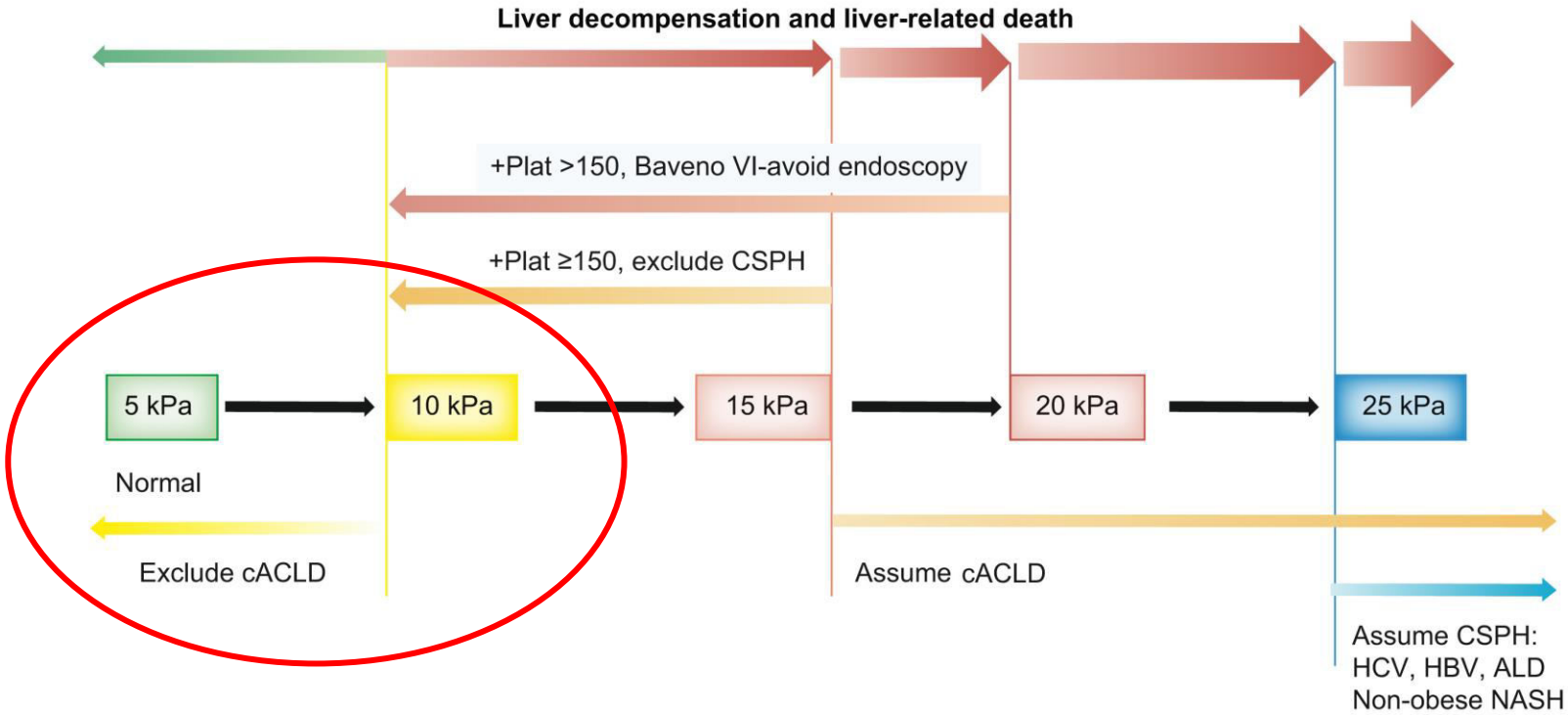
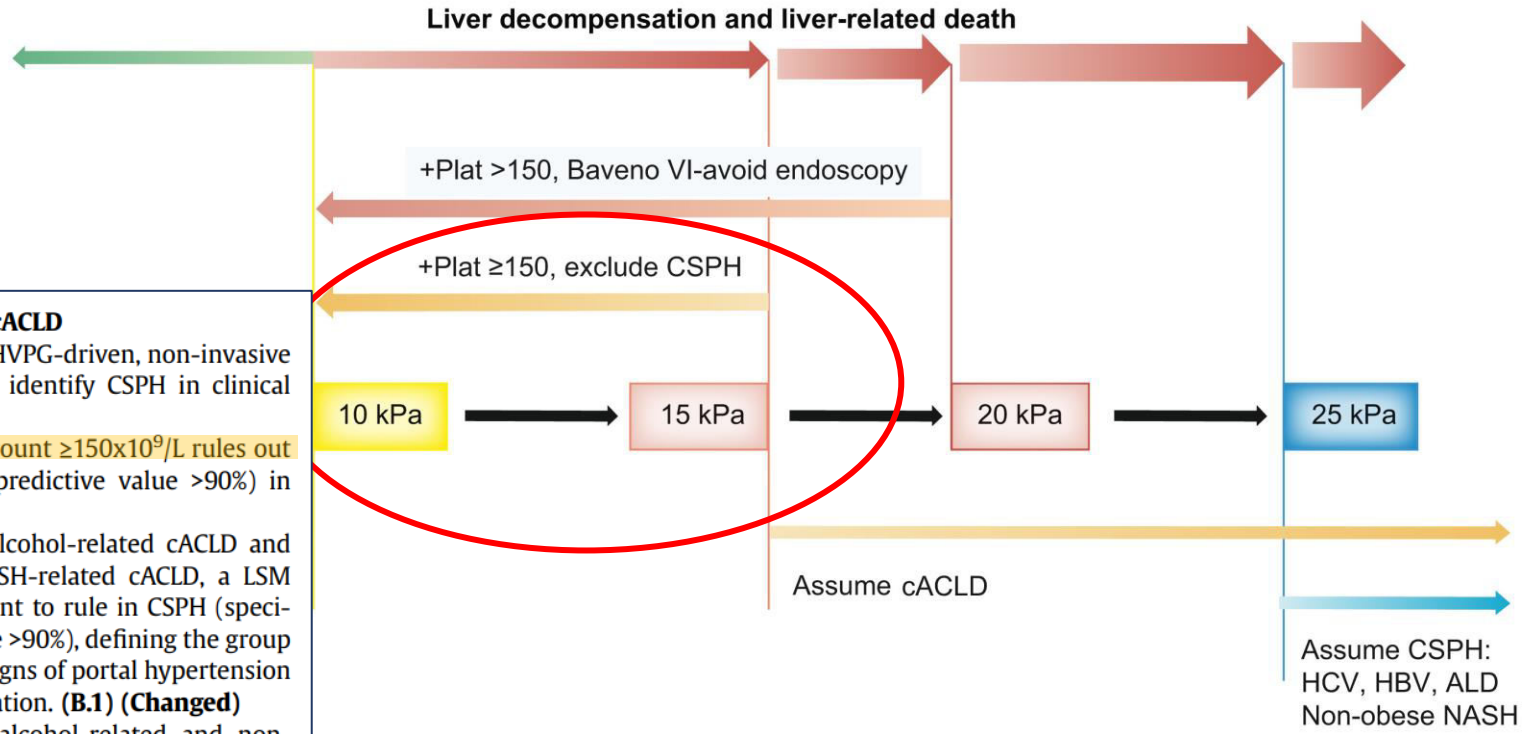


Roberto de Franchis et al (Baveno VII faculty), J Hepatol 2022

Diagnosis of clinically significant portal hypertension

„Rule of five“



Diagnosis of CSPH in patients with cACLD

2.14 Although the concept of CSPH is HVPG-driven, non-invasive tests are sufficiently accurate to identify CSPH in clinical practice. **(A.1) (New)**

2.15 LSM by TE ≤15 kPa plus platelet count ≥150x10^9/L rules out CSPH (sensitivity and negative predictive value >90%) in patients with cACLD. **(B.2) (New)**

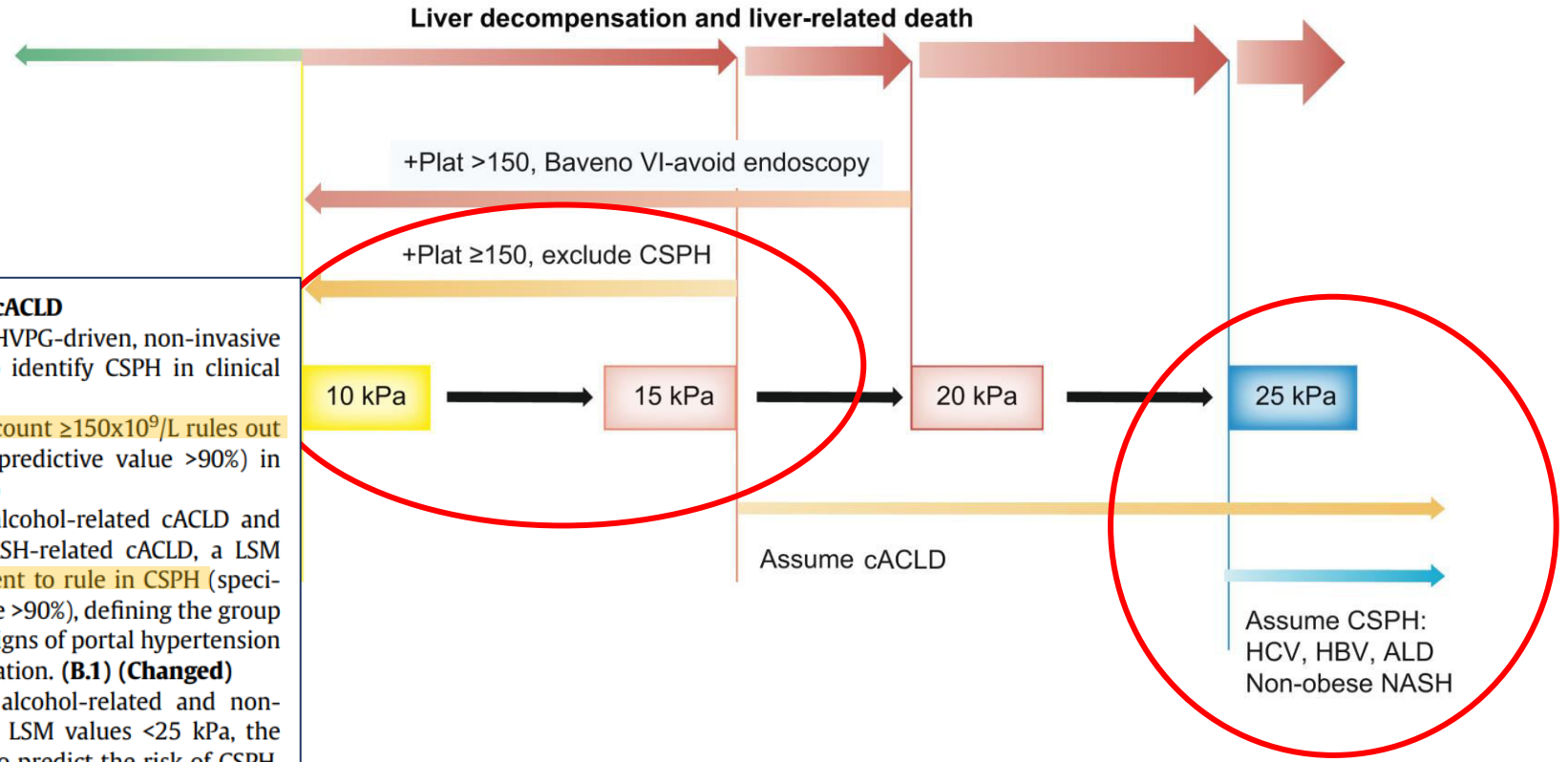
2.16 In patients with virus- and/or alcohol-related cACLD and non-obese (BMI <30 kg/m^2) NASH-related cACLD, a LSM value by TE of ≥25 kPa is sufficient to rule in CSPH (specificity and positive predictive value >90%), defining the group of patients at risk of endoscopic signs of portal hypertension and at higher risk of decompensation. **(B.1) (Changed)**

2.17 In patients with virus- and/or alcohol-related and non-obese NASH-related cACLD with LSM values <25 kPa, the ANTICIPATE model can be used to predict the risk of CSPH. Based on this model, patients with LSM values between 20-25 kPa and platelet count <150x10^9/L or LSM values between 15-20 kPa and platelet count <110x10^9/L have a CSPH risk of at least 60%. **(B.2) (New)**

Roberto de Franchis et al (Baveno VII faculty), J Hepatol 2022

Diagnosis of clinically significant portal hypertension

„Rule of five“



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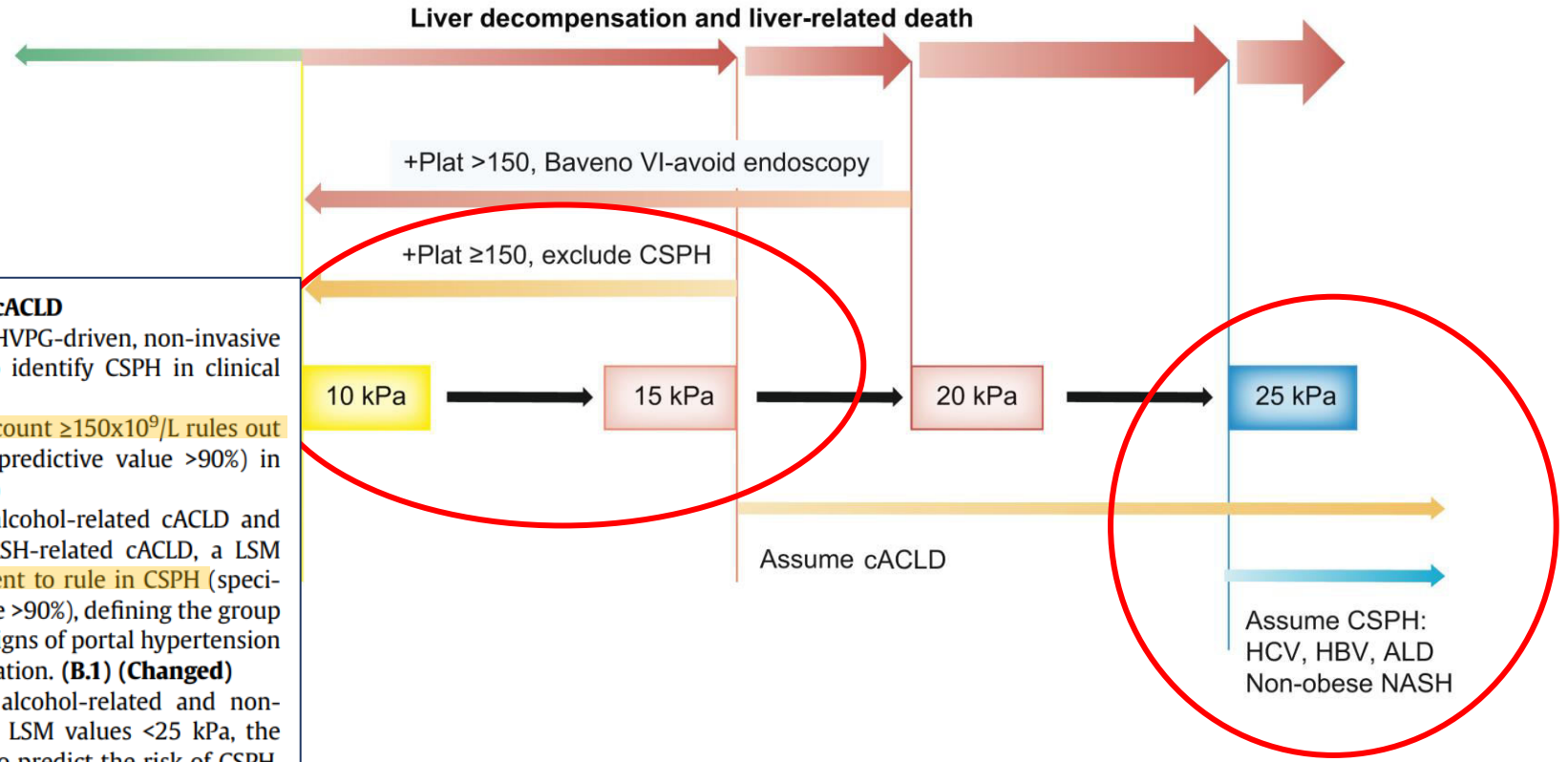

Diagnosis of CSPH in patients with cACLD

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2.15 LSM by TE ≤15 kPa plus platelet count ≥150x10^9/L rules out CSPH (sensitivity and negative predictive value >90%) in patients with cACLD. **(B.2) (New)**

2.16 In patients with virus- and/or alcohol-related cACLD and non-obese (BMI <30 kg/m^2) NASH-related cACLD, a LSM value by TE of ≥25 kPa is sufficient to rule in CSPH (specificity and positive predictive value >90%), defining the group of patients at risk of endoscopic signs of portal hypertension and at higher risk of decompensation. **(B.1) (Changed)**

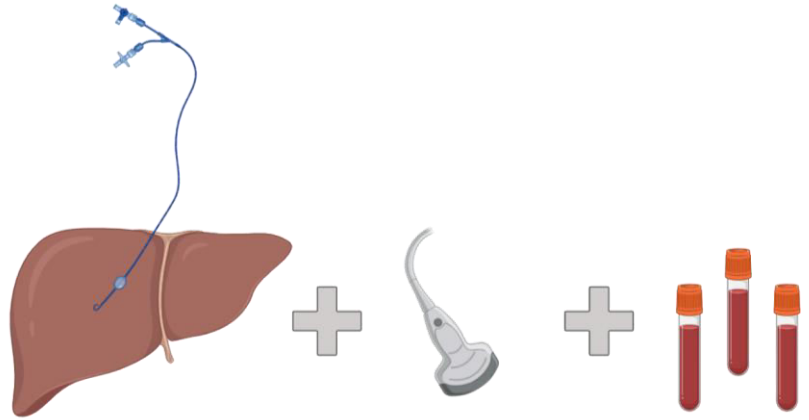
2.17 In patients with virus- and/or alcohol-related and non-obese NASH-related cACLD with LSM values <25 kPa, the ANTICIPATE model can be used to predict the risk of CSPH. Based on this model, patients with LSM values between 20-25 kPa and platelet count <150x10^9/L or LSM values between 15-20 kPa and platelet count <110x10^9/L have a CSPH risk of at least 60%. **(B.2) (New)**

➢ **What about HDV?**

Roberto de Franchis et al (Baveno VII faculty), J Hepatol 2022

Baveno VII criteria in chronic HDV infection

51 patients with chronic HDV infection and cACLD



HVPG + Liver/Spleen stiffness + Laboratory values

92 patients with chronic HDV infection and cACLD

Liver/Spleen stiffness + Laboratory values

Evaluation of NITs for the prediction of CSPH

- LSM
- ANTICIPATE model (LSM + platelets)
- VITRO score (vWF/platelet ratio)
- SSM

Prognostic value of NITs (validation cohort)

- Hepatic decompensation within 2 years

Jachs M, Sandmann L*, et al. J Hepatol. 2024 Aug;81(2):248-257.*
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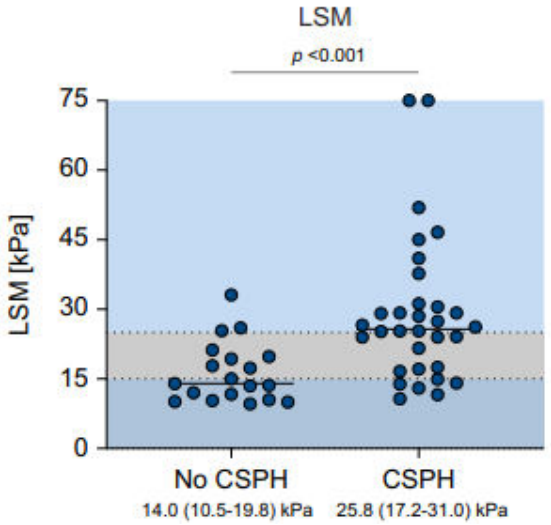
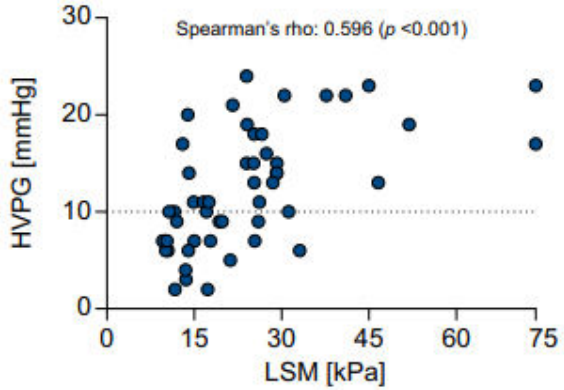
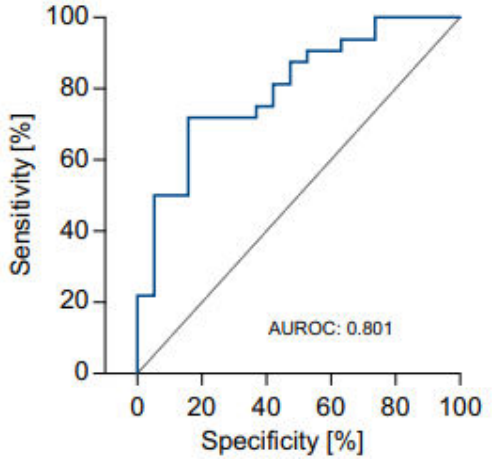
NITs accurately predict CSPH in CHD







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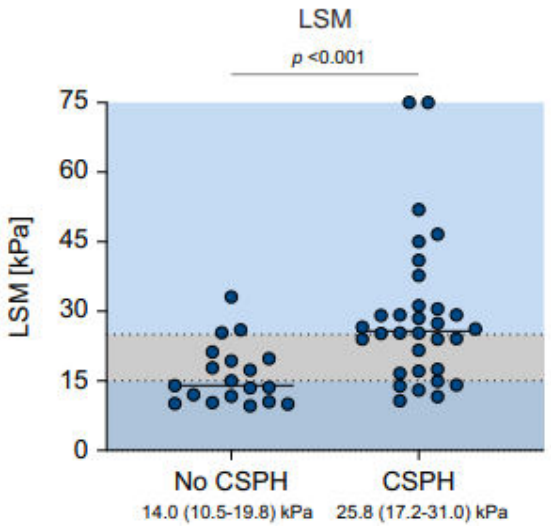
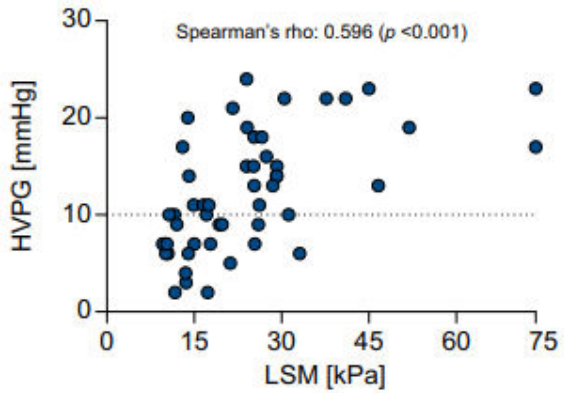
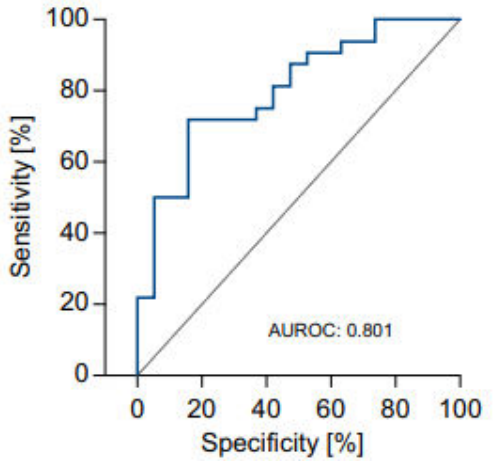
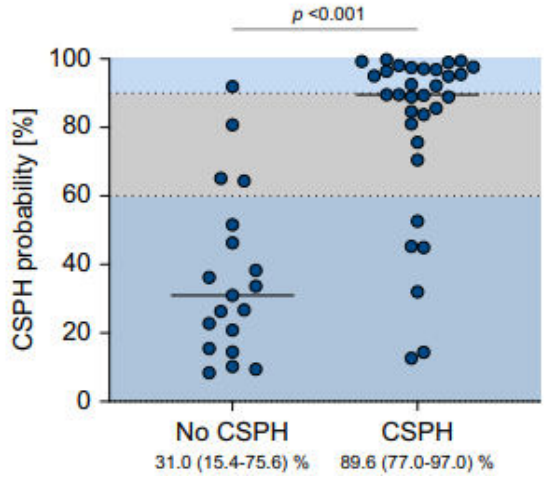
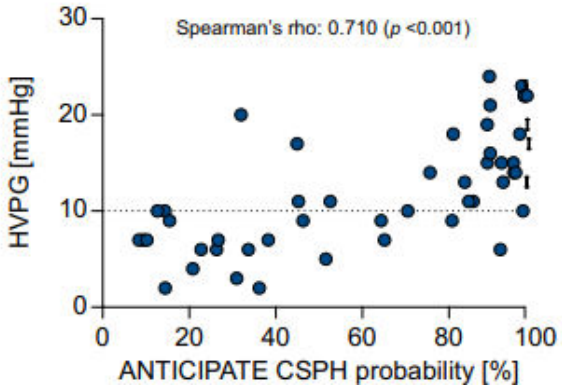


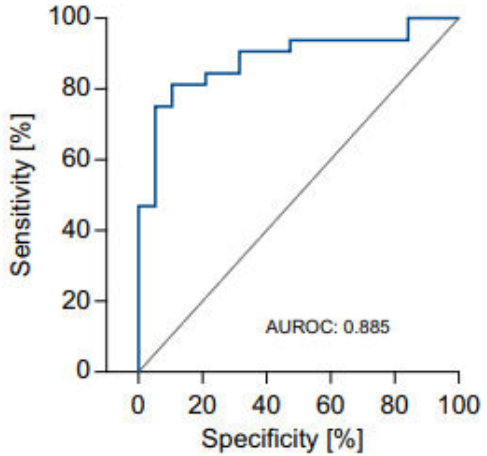




ANTICIPATE = LSM and platelets







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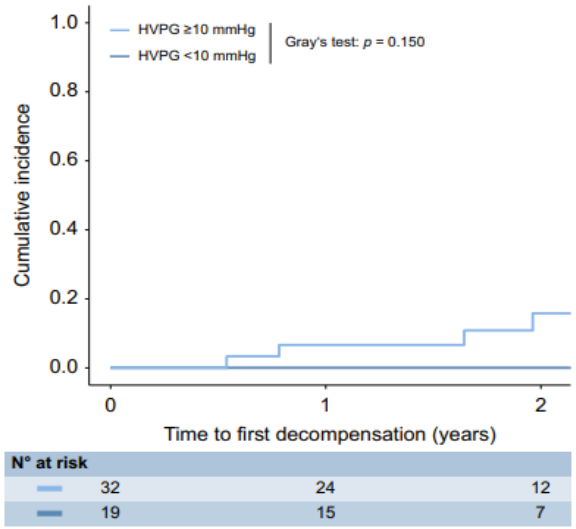
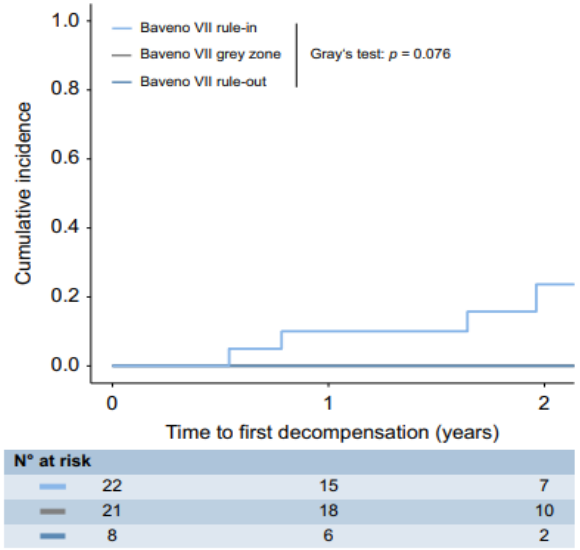
Confirmation of prognostic utility of HVPG and NITs

Derivation cohort





- Hepatic decompensation within 2 years occurred exclusively in CSPH

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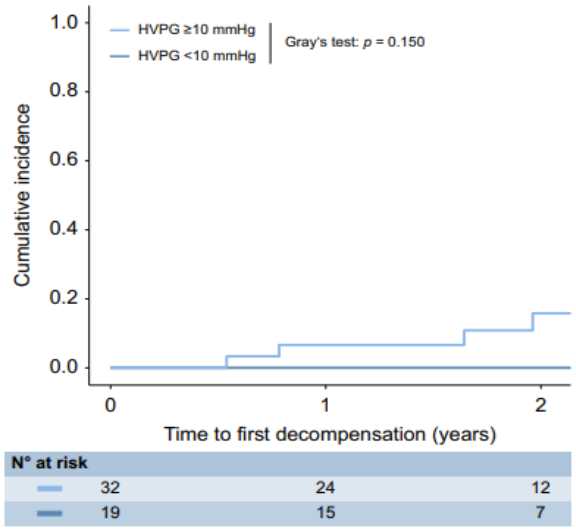
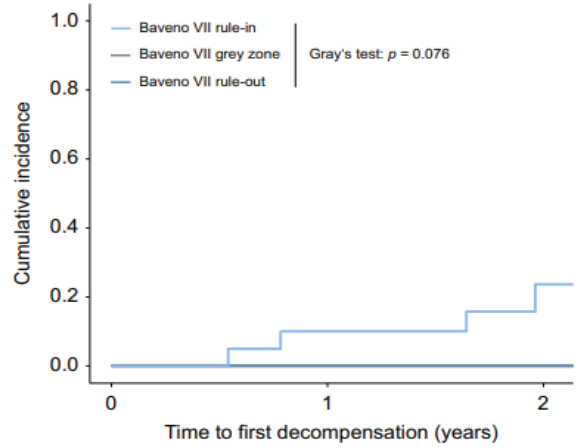
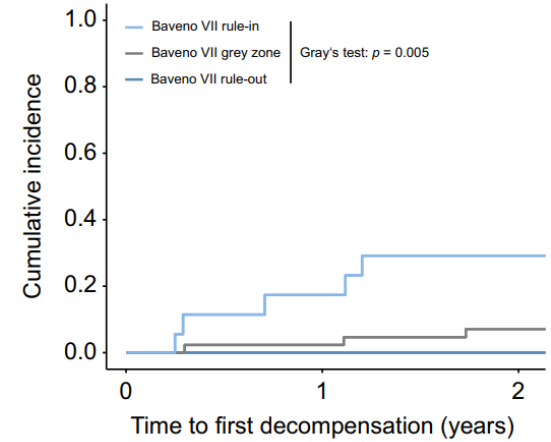


N° at risk			
	32	24	12
	19	15	7

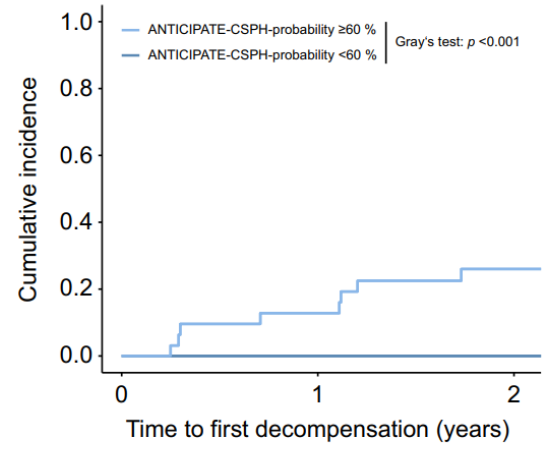


N° at risk			
	22	15	7
	21	18	10
	8	6	2

Validation cohort



N° at risk			
	19	14	10
	47	42	34
	26	21	18



N° at risk			
	35	27	21
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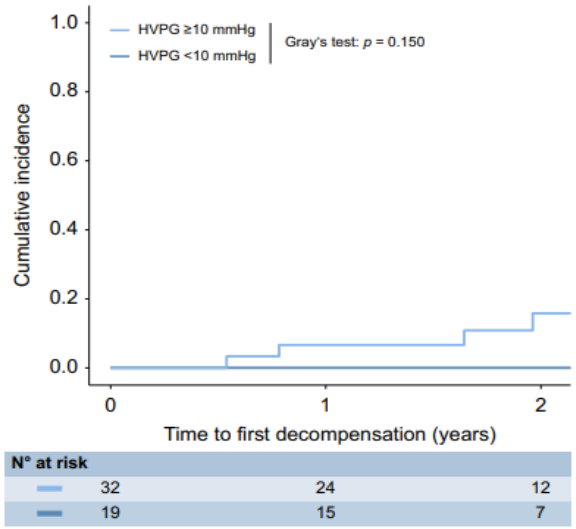

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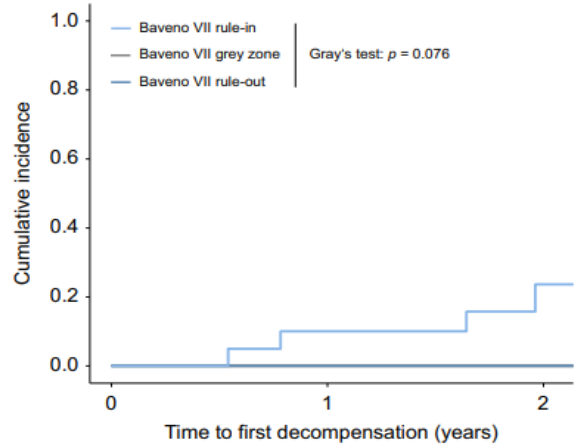

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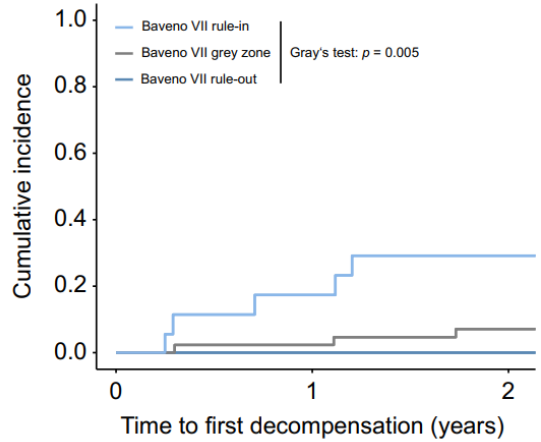

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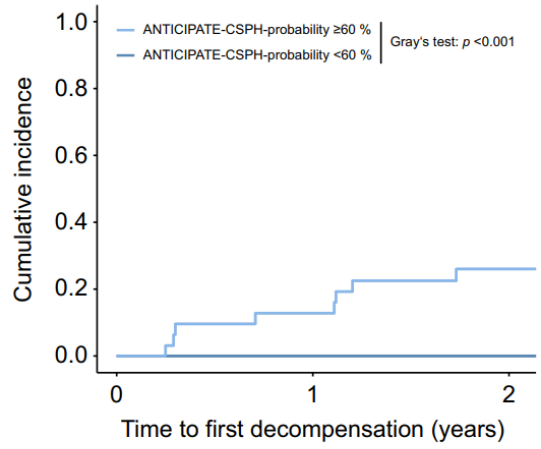

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- Hepatic decompensation within 2 years occurred exclusively in patietns with CSPH

- NITs for CSPH can be applied in HDV-cACLD with high accuracy
- NITs have similar ability as HVPG to identify high-risk patients with HDV-cACLD

Gastroenterology Hepatology Infectious Diseases Endocrinology

D-SOLVE

DZIF Deutsches Zentrum für Infektionsforschung

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Hannover Medical School

Conclusion

- Staging of liver disease is important for risk stratification of patients.
- Non-invasive tests can be used to rule out advanced chronic liver disease, also in CHD.

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- Patients with HDV-cACLD at high risk for liver-related events can be identified by NITs.

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- Non-invasive tests can be used to rule out advanced chronic liver disease, also in CHD.
- Clinically significant portal hypertension can be diagnosed with high accuracy by NITs.
- Patients with HDV-cACLD at high risk for liver-related events can be identified by NITs.
- NITs cannot completely replace liver biopsies, as additional information (e.g. features of autoimmunity) can only be evaluated by liver biopsy.