MÁSTER EN HEPATOLOGÍA

Universidad Autónoma de Madrid

Universidad de Alcalá

Asignatura: Problemas clínicos y controversias en hepatología

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Compensated and decompensated ACLD/cirrhosis after removal/suppression of the primary aetiological factor

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cACLD

Overt HE

- Component of ACLF

- Usually late-stage decompensation
- Risk likely decreased if bleeding/ascites is prevented

Fibrosis

- Chronic liver injury and inflammation
- Fibrogenesis and accumulation of ECM
- Parenchymal loss-of-function

- Weight loss and physical exercise

- Etiological therapies (e.g., antivirals, UDCA for PBC, obeticholc acid for NASH)

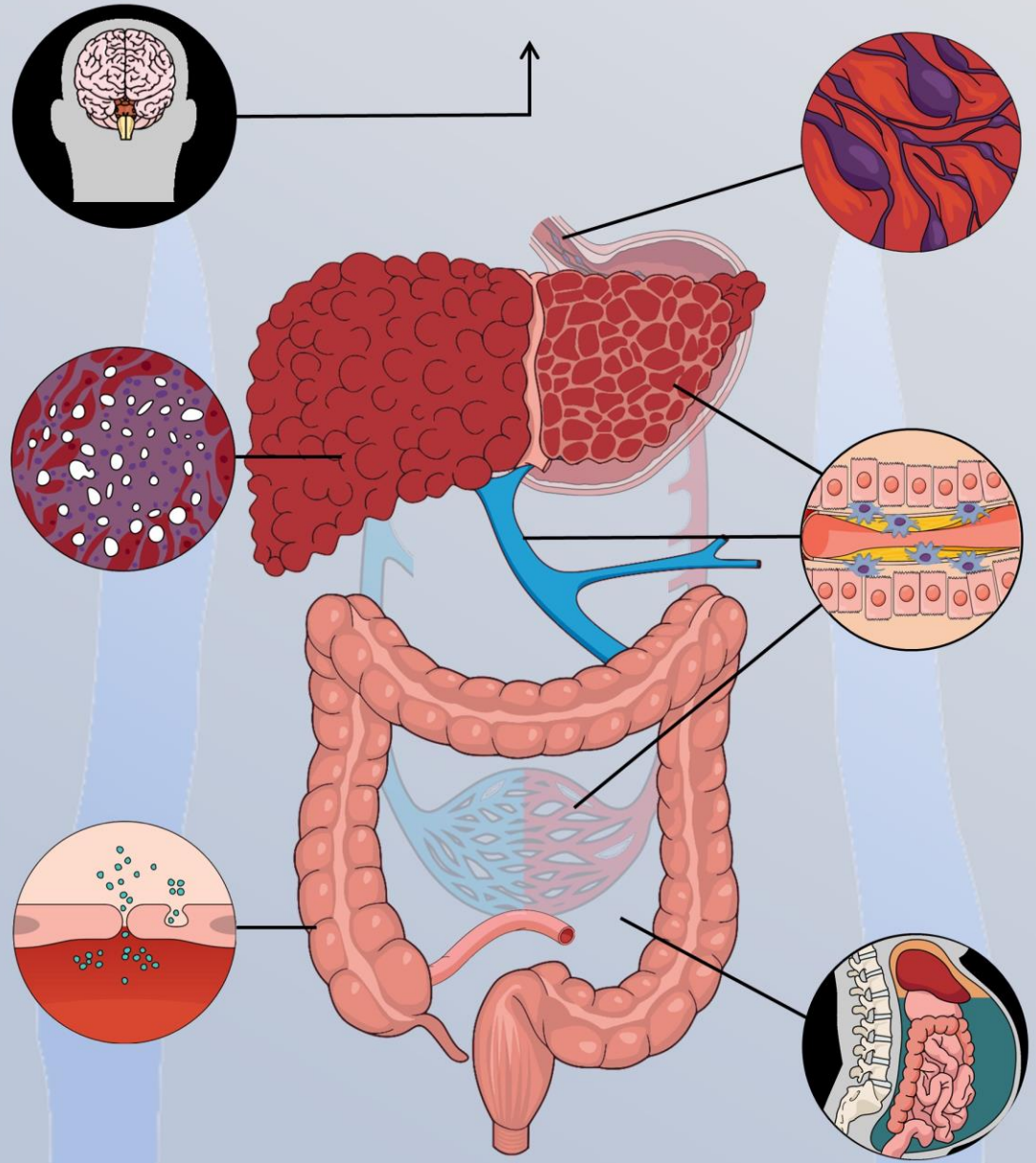
- Efficacy of obeticholic acid in compensated NASH cirrhosis
- Efficacy of other emerging therapies for NASH/PBC

Systemic inflammation

- Bacterial translocation from the gut
- Promotes endothelial dysfunction, fibrogenesis, and arterial vasodilation

- Norfloxacin and albumin - unsuitable for preventing first decompensation
- Non-selective betablockers

- Efficacy of modulators of the gut-liver axis



Variceal bleeding

- Trigger of ACLF

- Prevented by primary prophylaxis
- Incidence particularly low in HVPG-responders to NSBB

Portal hypertension

- Increased intrahepatic resistance
  (I) Structural component (see fibrosis)
  (II) Dynamic component (hepatic vascular tone)
  Hyperdynamic circulation

- Sustained alcohol abstinence
- Weight loss and physical exercise

- Etiological therapies (e.g., antiviral therapies and UDCA for PBC)

of intrahepatic resistance and hyperdynamic circulation)
- Propranolol/nadolol (targeting hyperdynamic circulation)
- Statins
- Taurine et al.

- Efficacy of emerging therapies for NASH
- Efficacy of poorly absorbable antibiotics (unsuitable for preventing first decompensation)

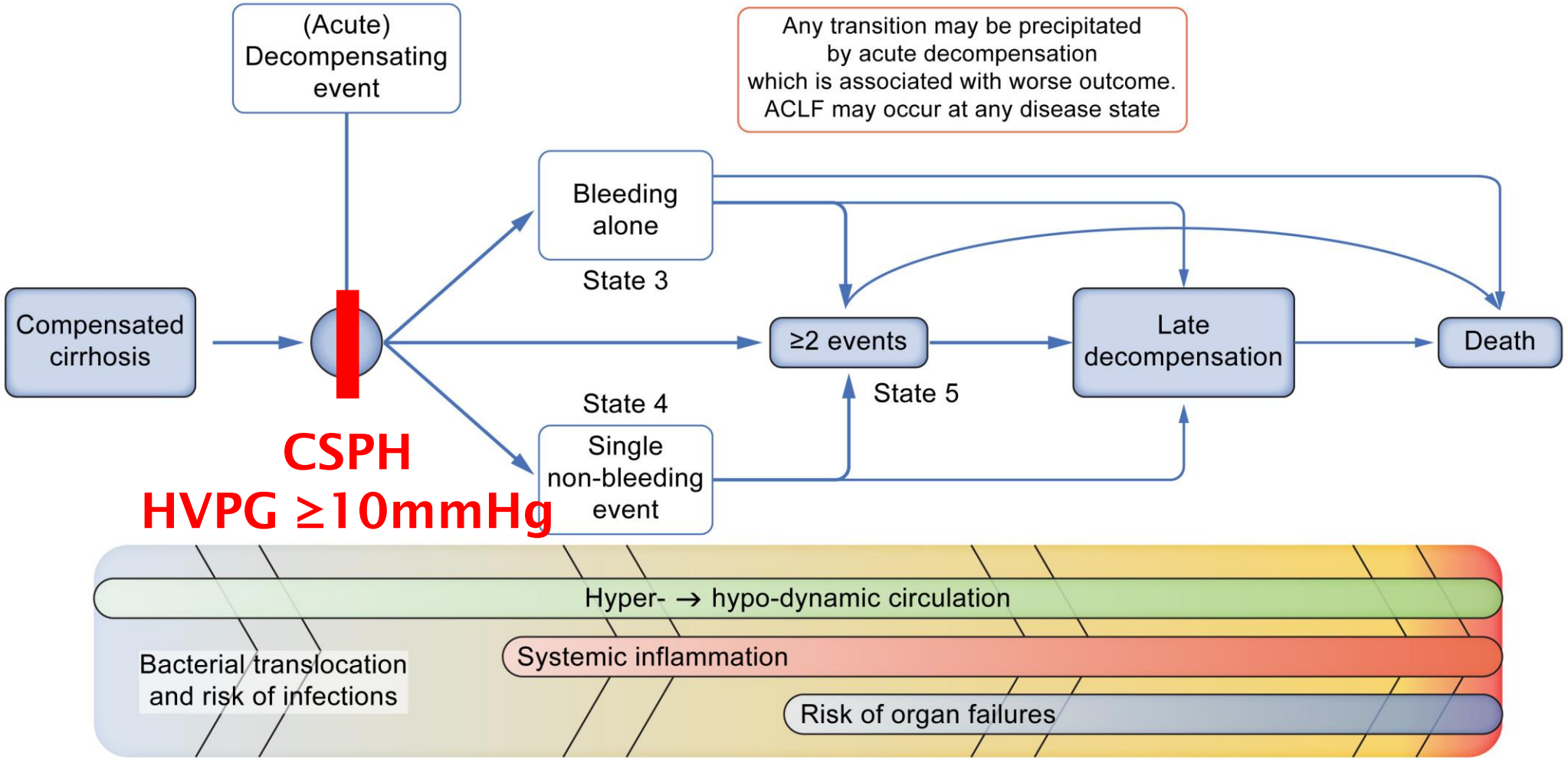
Ascites

- RA, SBP, and HRS-AKI/-NAKI

- Most common first decompensation
- Prevented by HVPG-guided NSBB therapy (or carvedilol)
- Incidence particularly low in HVPG-responders

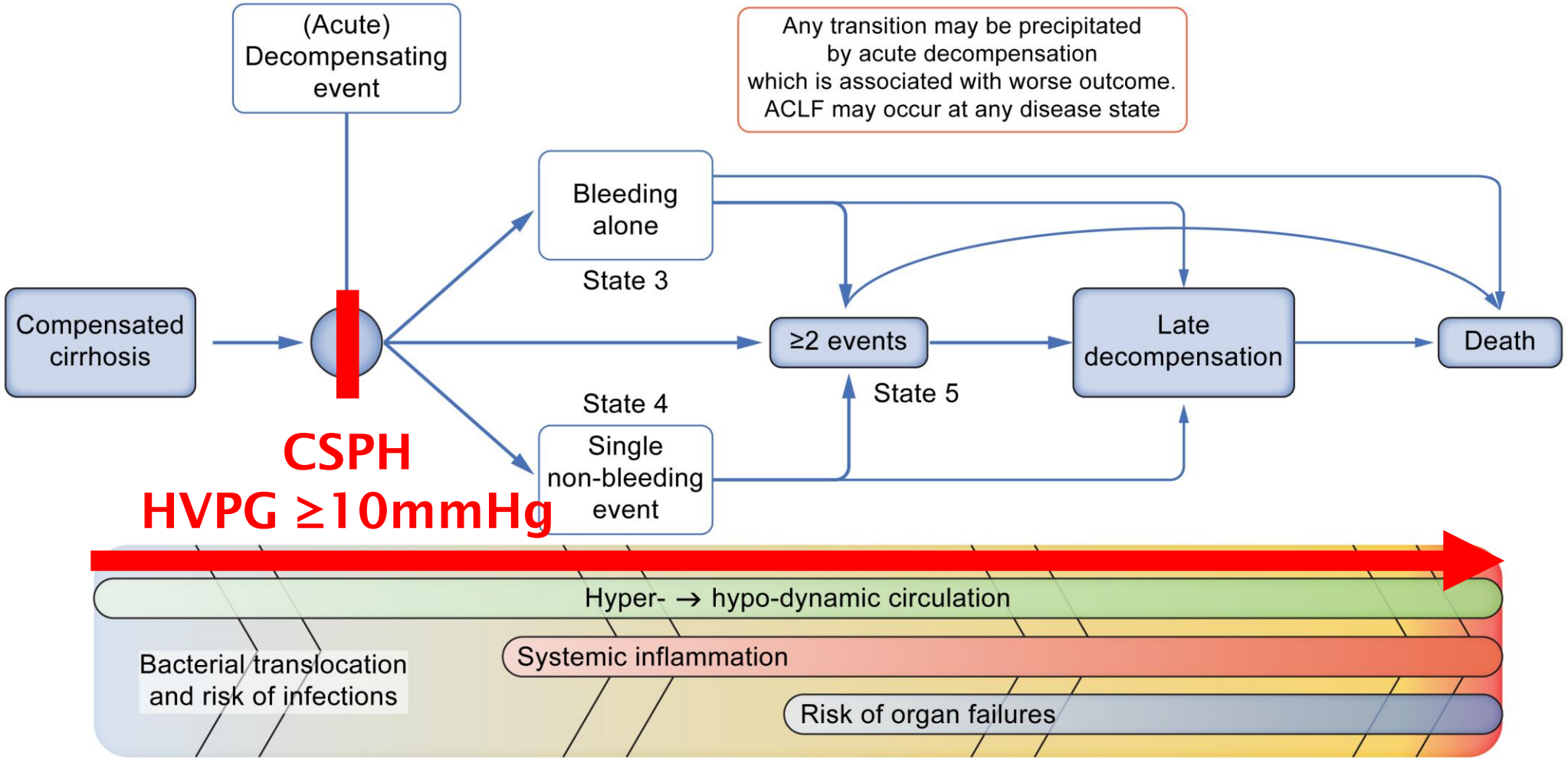
Decompensation events | Drivers of decompensation | Decisive pathomechanisms | Complications | Lifestyle interventions | Effective treatment | Summary | Further data required

Haemodynamic threshold for decompensation



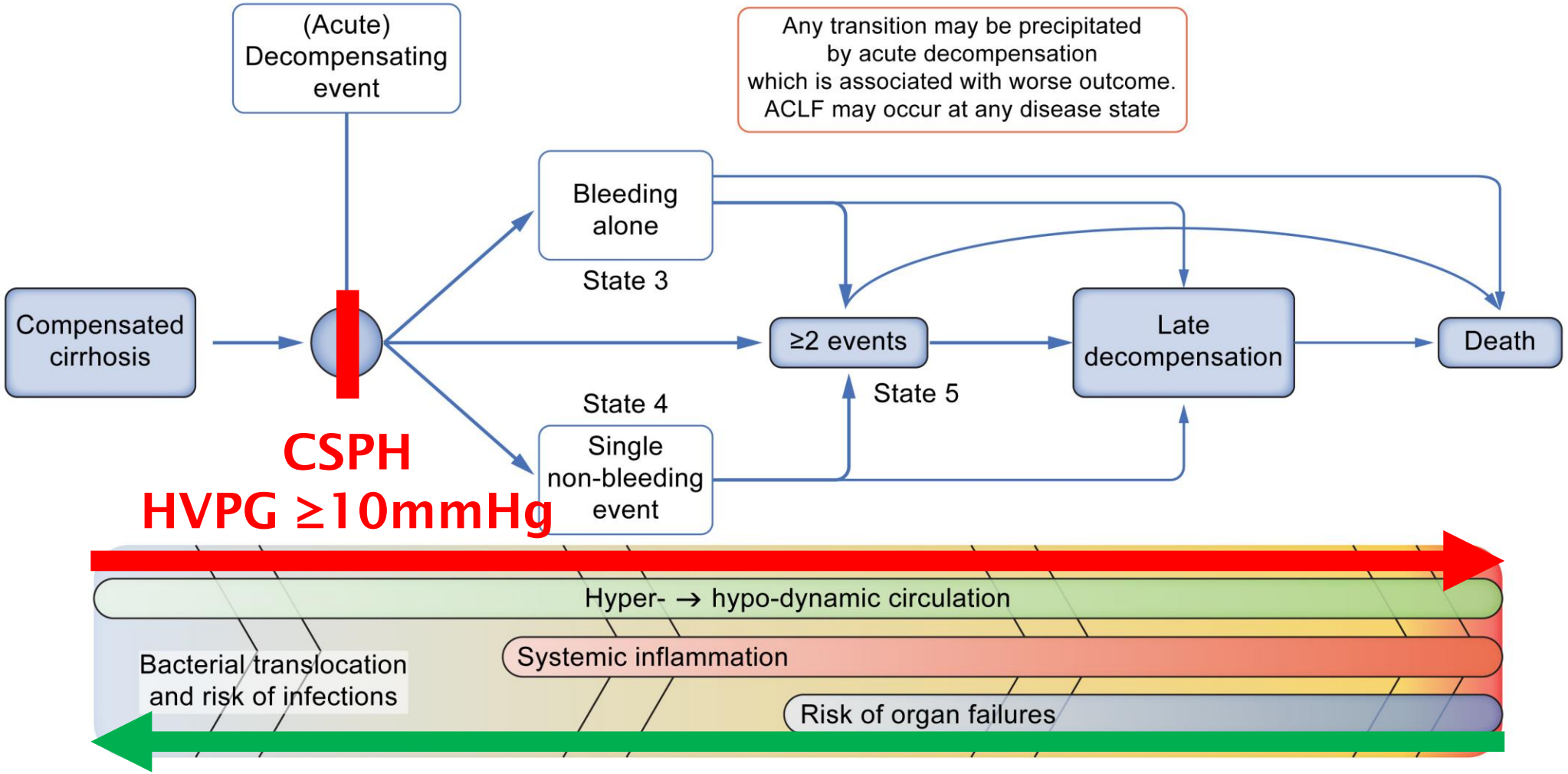
Jalan and D'Amico et al. J Hepatol 2021

Old perspective



Jalan and D'Amico et al. J Hepatol 2021

New perspective



Jalan and D'Amico et al. J Hepatol 2021

Recommendations #1

- **Removal/suppression of the primary aetiological factor** includes sustained virological response (**SVR**) in patients with **HCV infection**, **HBV suppression in the absence of HDV coinfection** in patients with chronic HBV infection, and **long-term abstinence from alcohol** in patients with **alcohol-related liver disease**. **(A.1) (New)**
- The **definition and impact** of the **removal/suppression of the primary aetiological factor** in **other ACLDs** is **less well established**. **(A.1) (New)**
- **Overweight/obesity, diabetes, and alcohol consumption** are important contributors to liver disease progression even after removal/suppression of the primary aetiological factor and should be addressed. **(A.1) (Changed)**

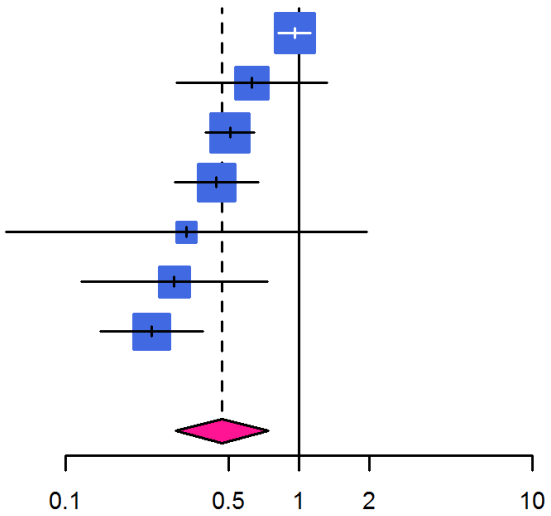
1. Baveno VII. J Hepatol 2022.

Impact of HBV suppression

Decompensation development

Study	NAs treated Events	NAs treated Total	Untreated Events	Untreated Total	RR	95%-CI	Weight
He, L 2019	374	923	117	276	0.96	[0.82; 1.12]	19.3%
Das, K 2010	13	453	14	306	0.63	[0.30; 1.32]	13.0%
Kim, CH 2012	59	240	234	481	0.51	[0.40; 0.64]	18.8%
Li, CZ 2013	23	79	25	38	0.44	[0.29; 0.67]	17.0%
Liaw, YF 2005	2	436	3	215	0.33	[0.06; 1.95]	4.9%
Liu, K 2019	8	797	10	291	0.29	[0.12; 0.73]	11.0%
Su,TH 2016	18	1350	77	1350	0.23	[0.14; 0.39]	15.9%
Random effects model		4278		2957	0.47	[0.30; 0.74]	100.0%

Heterogeneity: I^2 = 88%, τ^2 = 0.2758, p < 0.01
Test for overall effect: z = -3.25 (p < 0.01)



1. Preliminary/unpublished data.

Depending on their impact on surrogates/direct endpoints, which interventions/treatment outcomes should define etiological cure in patients with ALD or NAFLD-related cirrhosis (multiple answers possible)

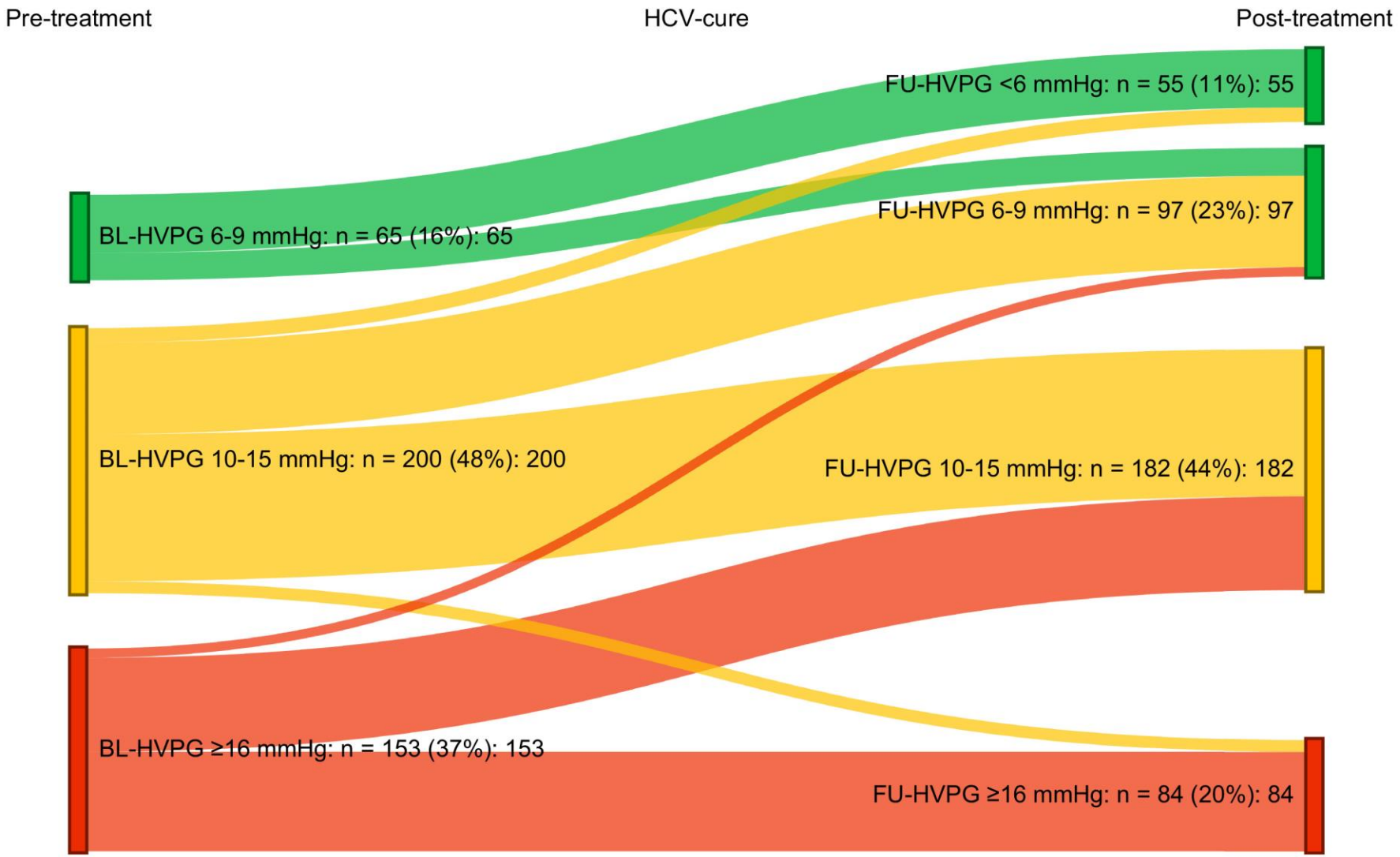
ANSWER CHOICES	RESPONSES	
Abstinence, i.e., no alcohol consumption in a patient with alcohol-related liver disease, irrespective of BMI.	63.64%	28
Abstinence, i.e., no alcohol consumption in a patient with alcohol-related liver disease and no obesity (BMI <30kg x m-2).	47.73%	21
A NAFLD patient achieving a total body weight loss of >10%.	45.45%	20
NASH resolution on follow-up liver biopsy.	54.55%	24
Total Respondents: 44		

Recommendations #2

- **Removal/suppression of the primary aetiological factor** leads to potentially meaningful **decreases in HVPG** in most patients and substantially **reduces the risk of hepatic decompensation**. **(A.1) (Changed)**
- **Absence/resolution of CSPH** following removal/suppression of the primary aetiological factor **prevents hepatic decompensation**. **(B.1) (Changed)**
- The optimal percent/absolute decrease in HVPG associated with a reduction in hepatic decompensation following the removal/suppression of the primary aetiological factor in patients with cACLD and CSPH has yet to be established. **(B.1) (New)**

1. Baveno VII. J Hepatol 2022.

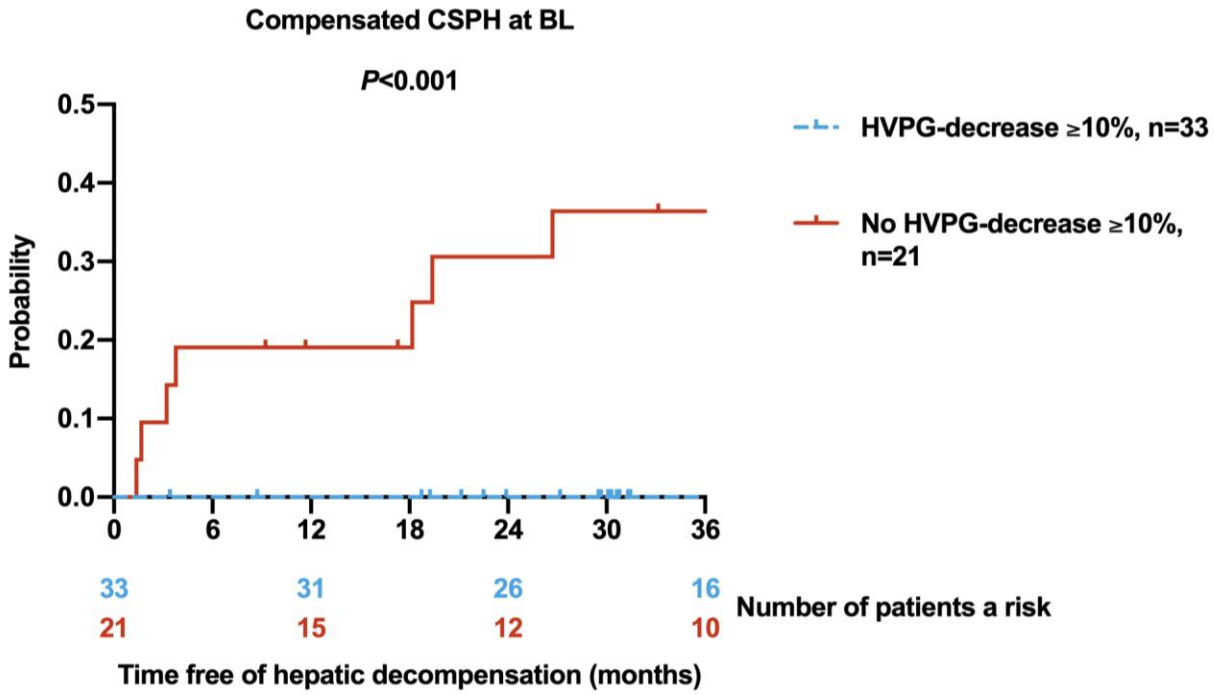
Evolution of portal hypertension after HCV-cure



Semmler and Lens et al. J Hepatol 2022

Management of ACLD after the removal of the primary aetiological factor: HVPG-decrease

≥10%-decrease protective (REF 1)



≥10%-decrease NOT protective (REF 2)

Not all patients abstinent (REF 3)

Simtuzumab (REF 4) ineffective, i.e., not considered as suppression/removal of the primary aetiological factor

1. Mandorfer et al. Hepatology 2020.
2. Lens and Baiges et al. J Hepatol 2021.
3. Vorobioff et al. Gastroenterology 1996.
4. Sanyal et al. Hepatology 2019.

Management of ACLD after the removal of the primary aetiological factor: HCV cure

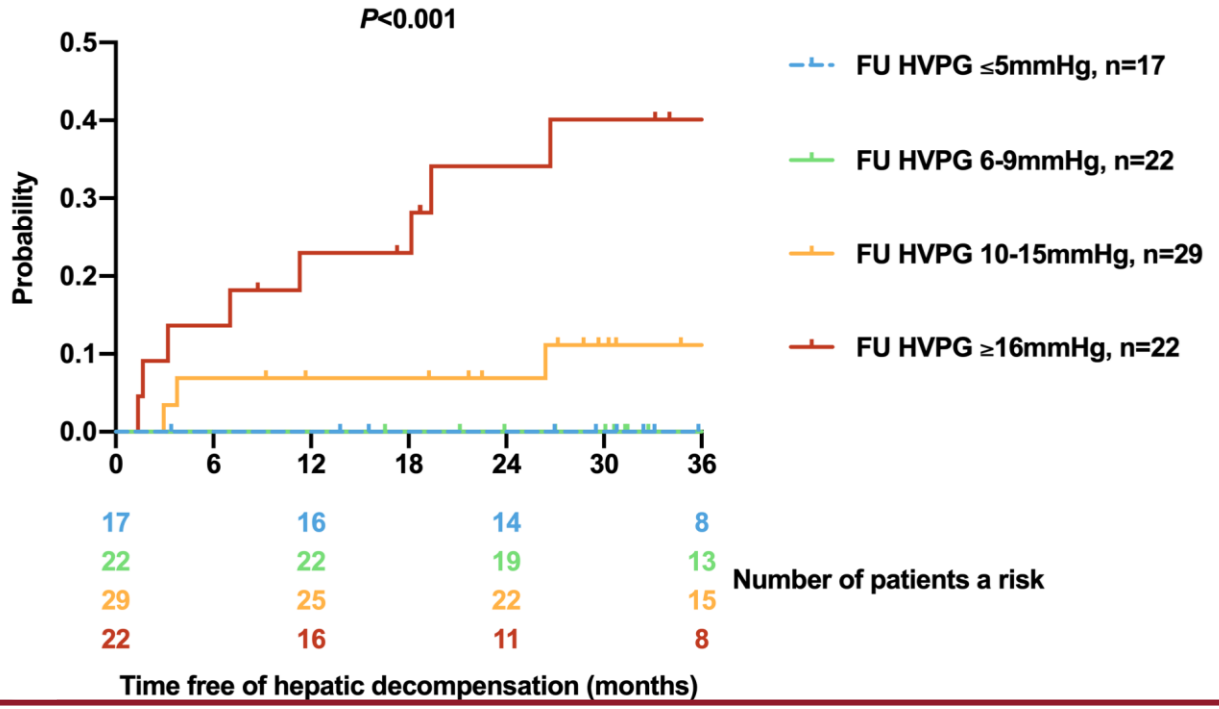
Overall, the incidence of hepatic decompensation following HCV-cure is low in cACLD patients:

- REF 1: 0.34/100 patient-years

…

- REF 2: 0.96/100 patient-years

However, a subset of patients remains at substantial risk (REF 3).



1. Pons et al. J Hepatol 2020.
2. Semmler et al. Hepatology 2021.
3. Mandorfer et al. Hepatology 2020.

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Personalized medicine!

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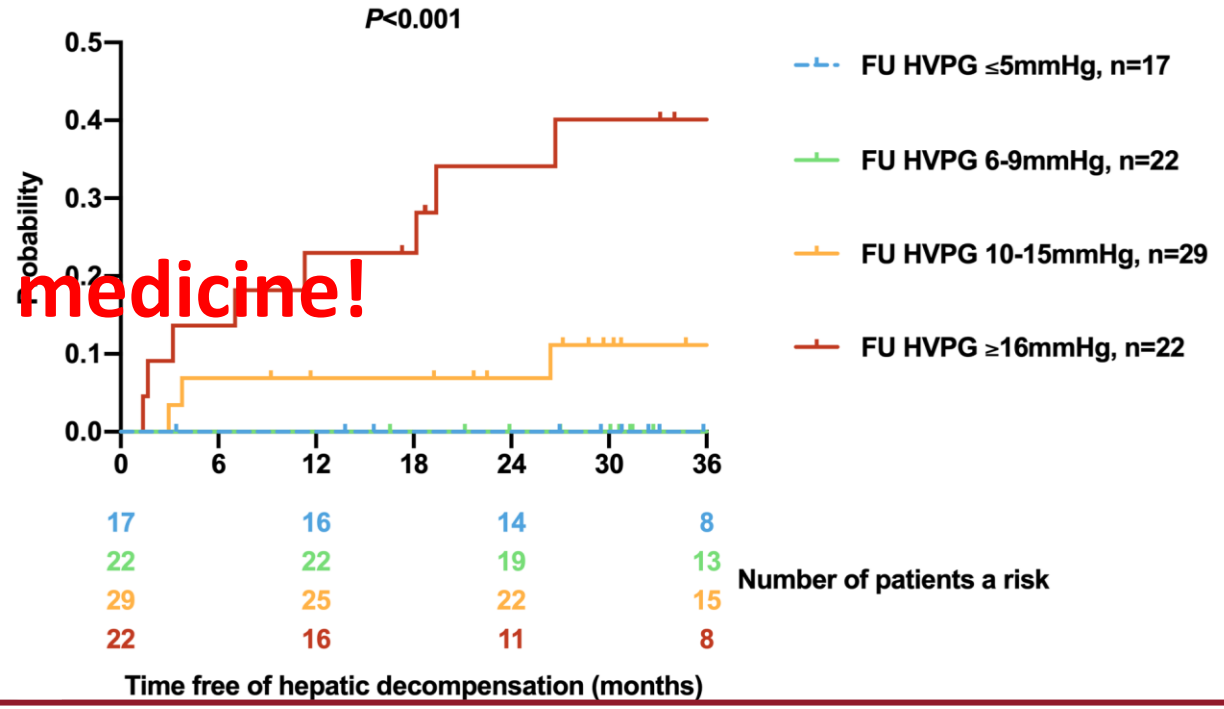
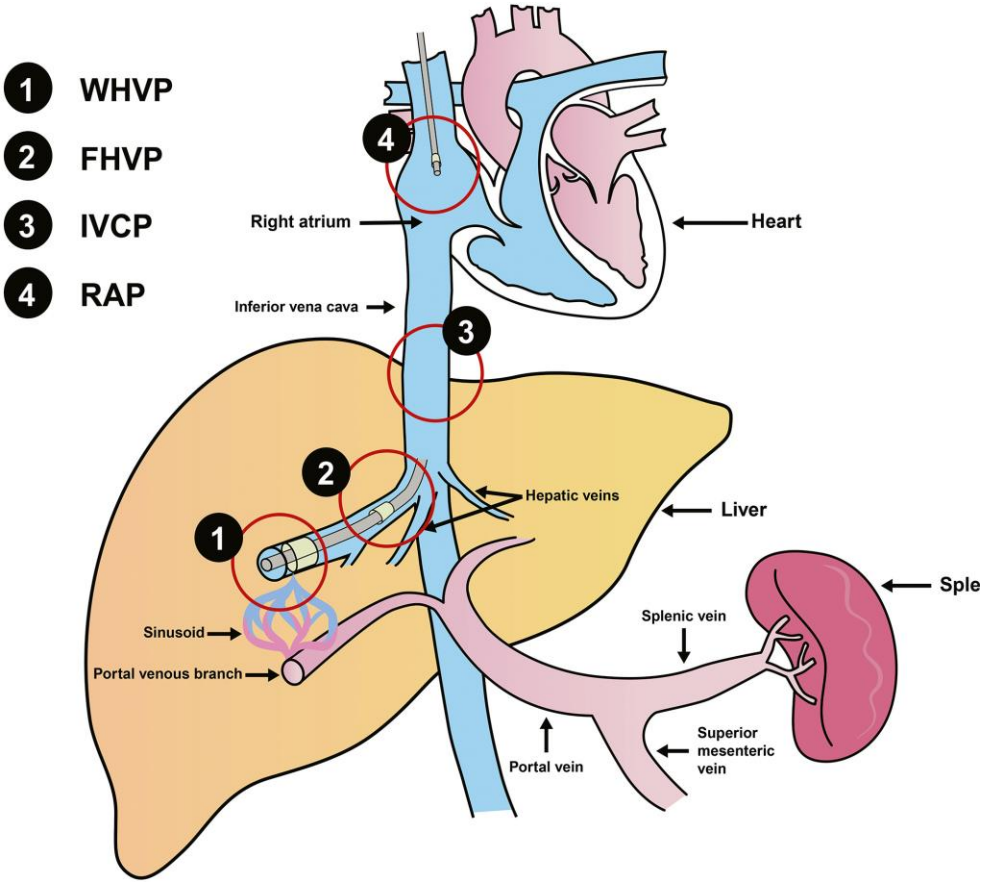
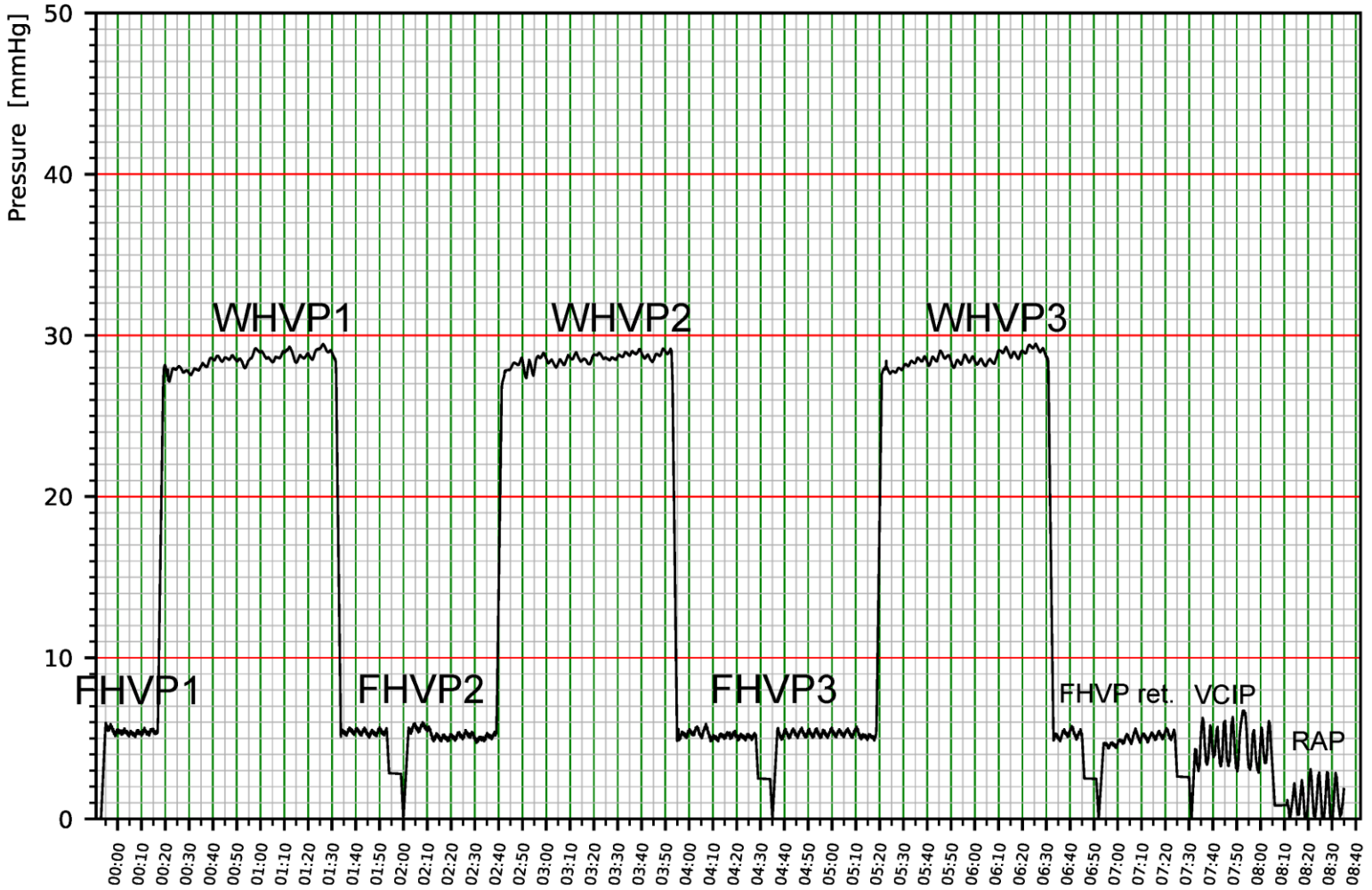


1. Pons et al. J Hepatol 2020
2. Semmler et al. Hepatology 2021
3. Mandorfer et al. Hepatology 2020

HVPG: The minimally invasive (imperfect) gold standard





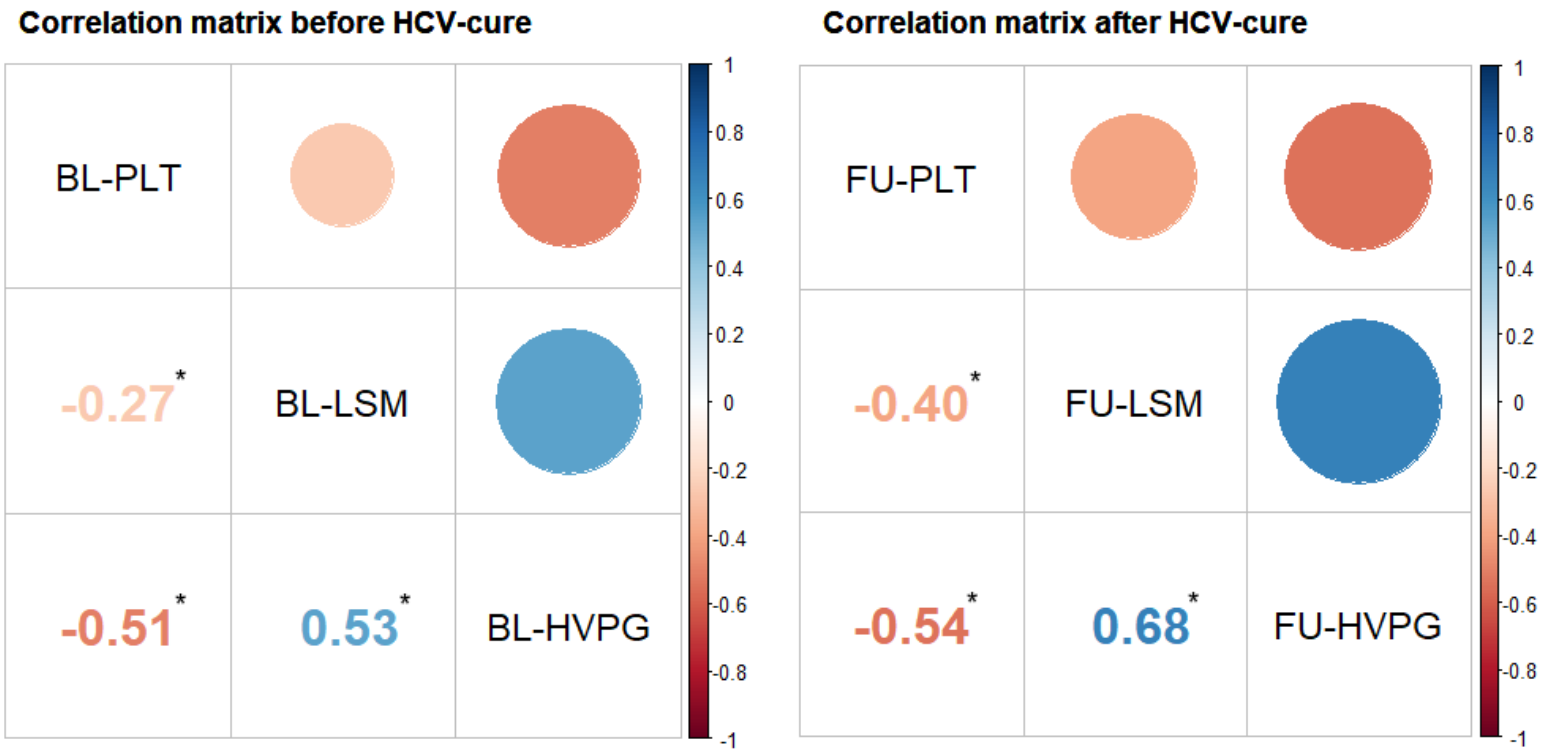
Reiberger et al. Hepatol Comm 2021; Vienna Hepatic Hemodynamic Lab

Recommendations #3

- In the **absence of co-factors**, patients with HCV-induced cACLD who achieve **SVR** and show **consistent post-treatment improvements** with **LSM values of <12 kPa and PLT >150x10^9/L** can be **discharged from portal hypertension surveillance (LSM and endoscopy)**, as they **do not have CSPH** and **are at negligible risk of hepatic decompensation**. In these patients, **HCC surveillance** should continue until further data is available. **(B.1) (New)**

1. Baveno VII. J Hepatol 2022.

Impact of HCV-cure on the correlation between HVPG/NIT



* p<0.001
BL-PLT/HVPG vs. FU-PLT/HVPG: p=0.613; BL-LSM/HVPG vs. FU-LSM/HVPG: p=0.012

1. Semmler and Lens et al. J Hepatol 2022

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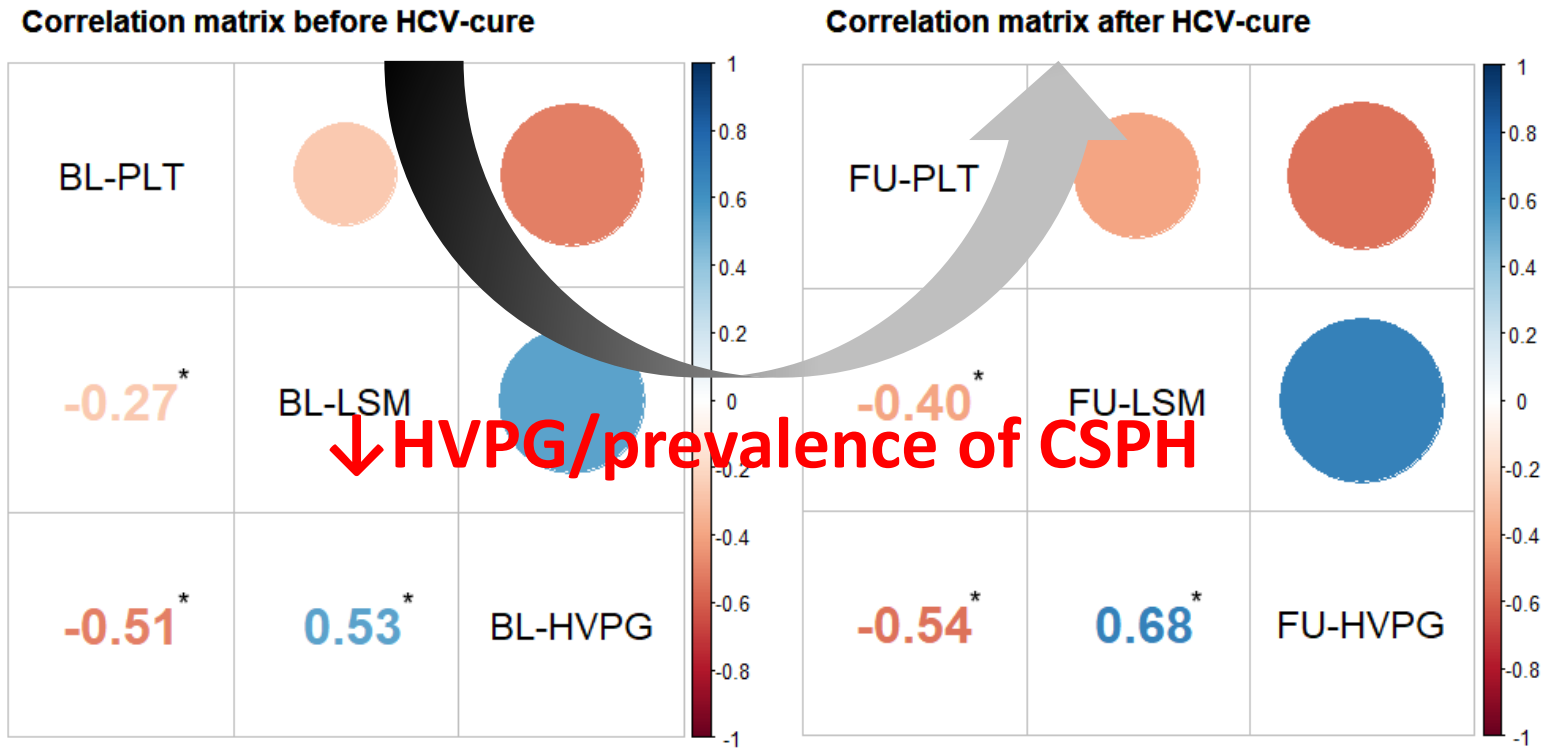

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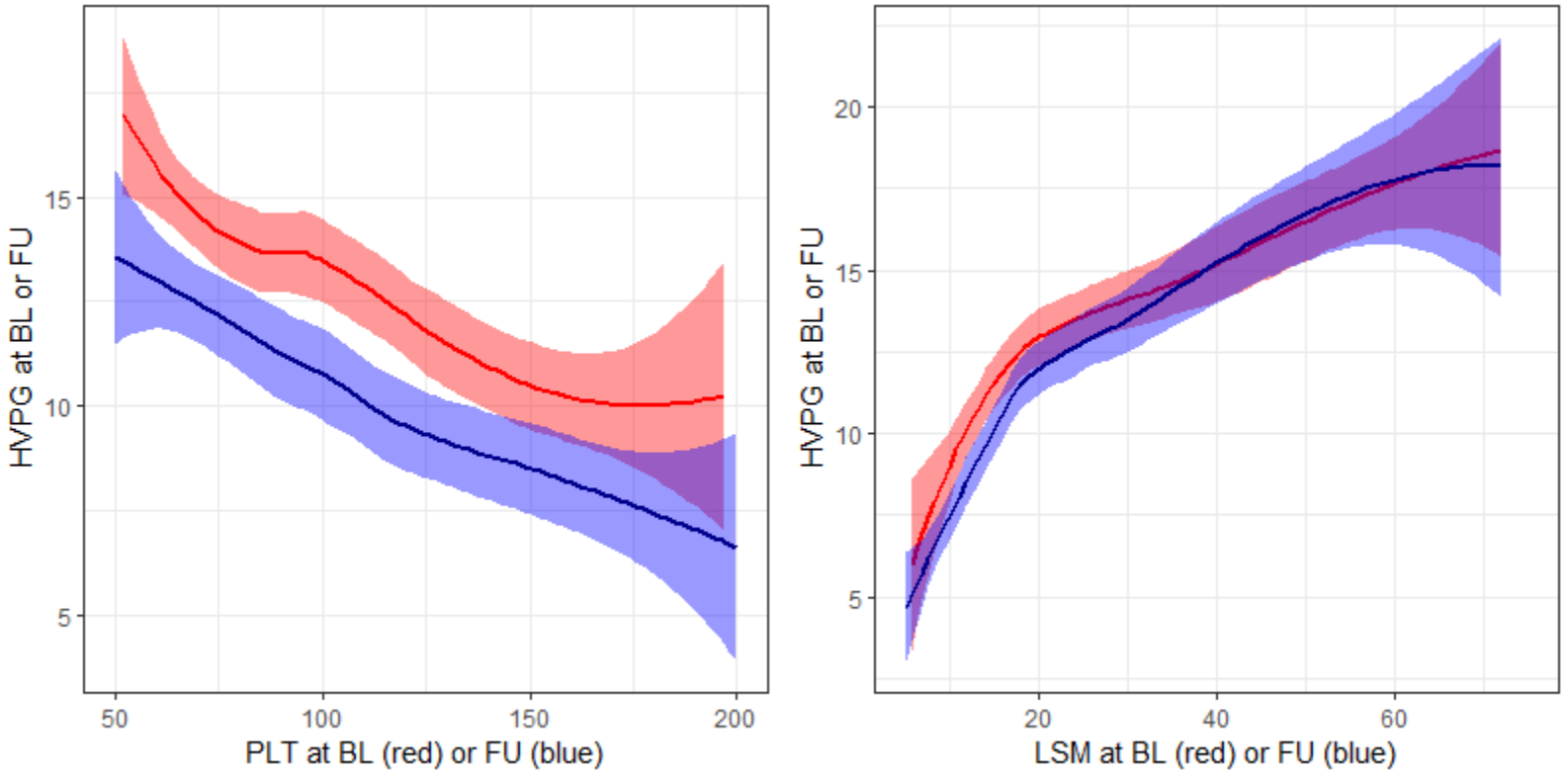
1. Semmler and Lens et al. J Hepatol 2022

Why do we need specific non-invasive criteria after HCV-cure?



1. Semmler and Lens et al. J Hepatol 2022

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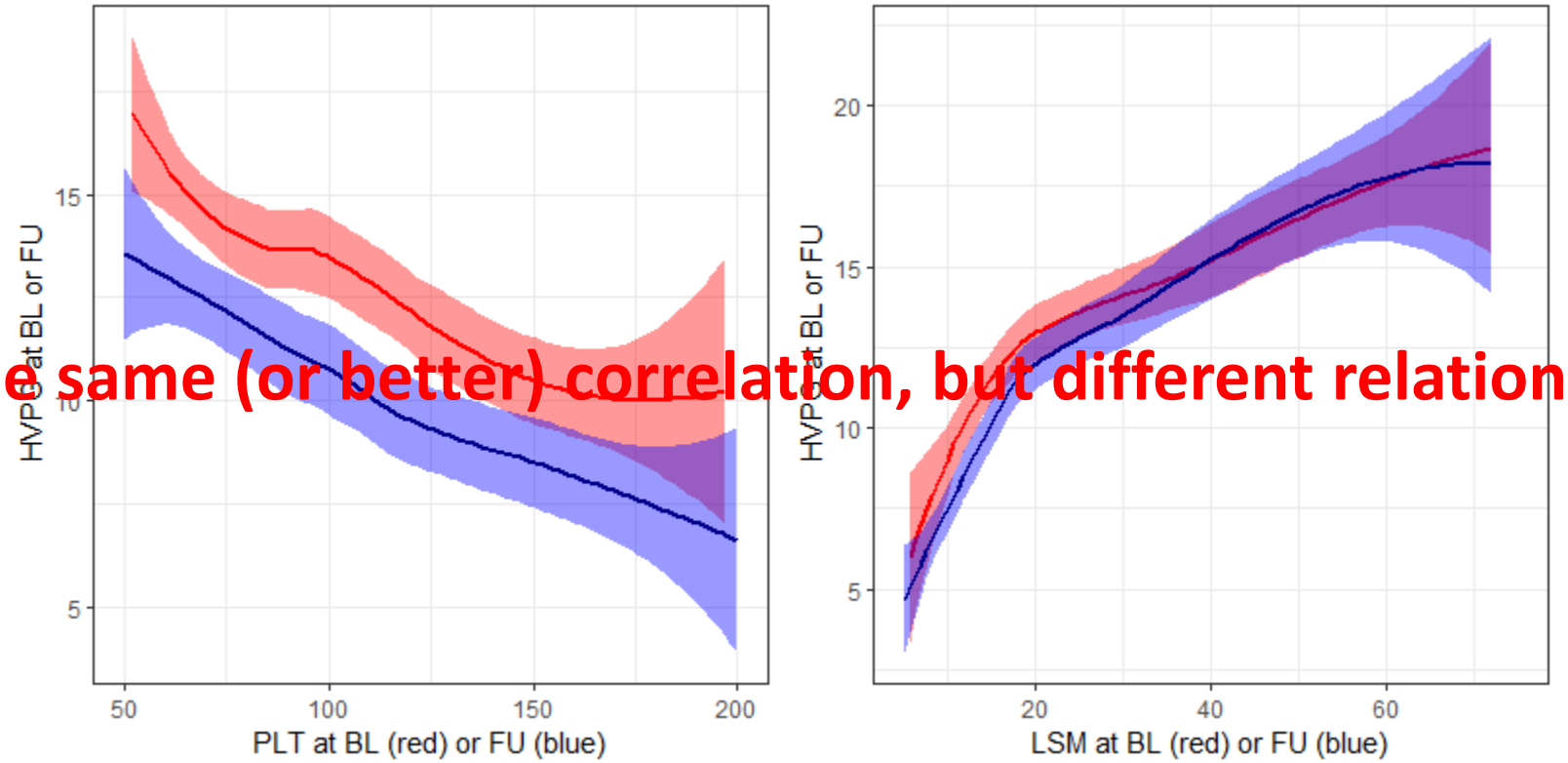


Same same (or better) correlation, but different relationship

1. Semmler and Lens et al. J Hepatol 2022

Excluding and ruling-in post-treatment CSPH

Variables	Outcome	AUC (95%CI)	Cut off (90% sensitive)	Cut off (90% specific)
cACLD subgroup				
BL-PLT	BL-CSPH	0.753 (0.677-0.828)	<170G/L	<70G/L
BL-LSM	BL-CSPH	0.831 (0.769-0.894)	>13.5kPa	>26.1kPa
BL-PLT+BL-LSM - linear	BL-CSPH	0.859 (0.807-0.912)	-	-
BL-PLT+BL-LSM - splines	BL-CSPH	0.883 (0.838-0.929)	-	-
FU-PLT	FU-CSPH	0.800 (0.745-0.855)	<144G/L	<77G/L
FU-LSM	FU-CSPH	0.837 (0.786-0.887)	>11.9kPa	>21.2kPa
FU-PLT+FU-LSM - linear	FU-CSPH	0.875 (0.831-0.920)	-	-
FU-PLT+FU-LSM - splines	FU-CSPH	**0.890 (0.850-0.930)**	-	-
FU-LSM<12kPa and FU-PLT>150G/L	FU-CSPH		**Sens: 99.2%**	Spec: 26.4%
FU-LSM>25kPa	FU-CSPH		Sens: 38.2%	**Spec: 93.6%**

1. Semmler and Lens et al. J Hepatol 2022

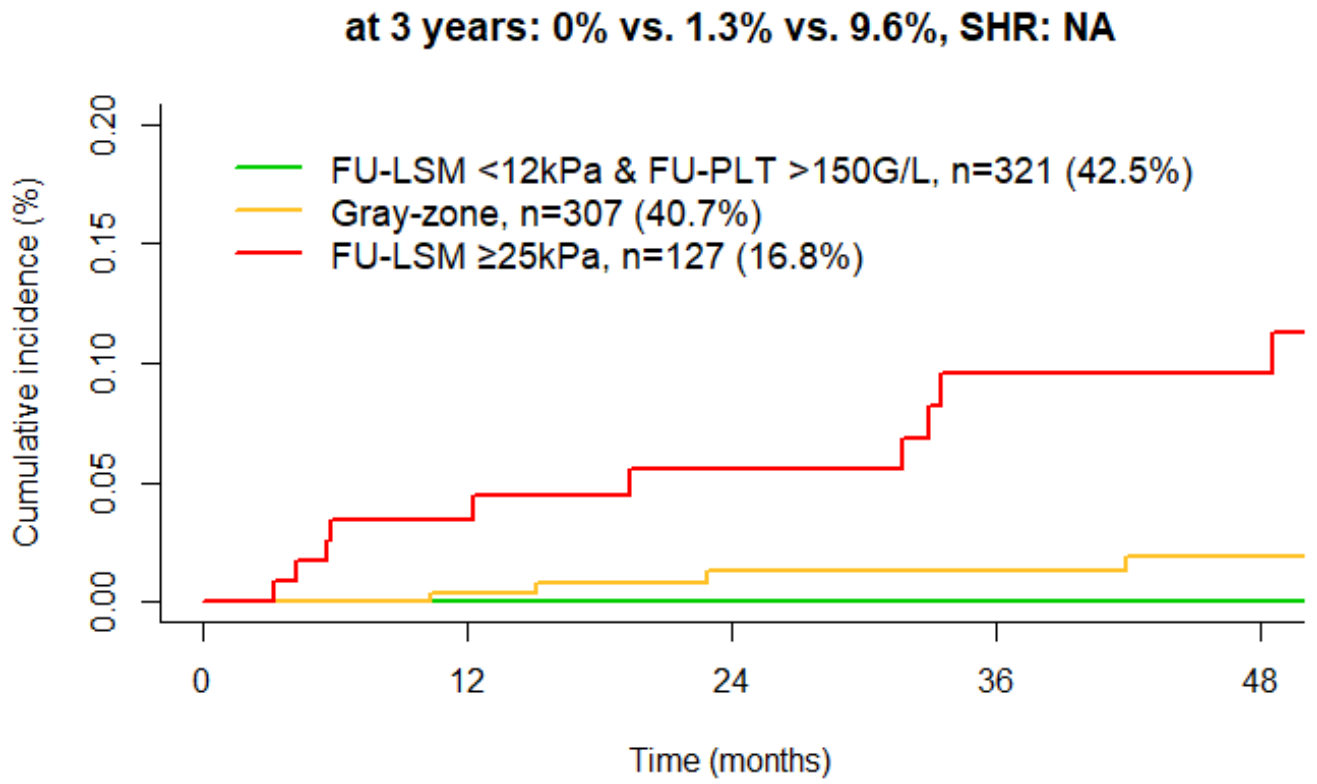
But do these strict criteria impact/facilitate patient management?

- Met by **42.5%** of **unselected cACLD patients with SVR** (based on an unpublished cohort of n=755 patients).
- Thus, a **relevant proportion of patients** can be **discharged from portal hypertension surveillance (NIT and endoscopy)** based on these criteria, **if no co-factors** are present.
- Cumulative porportion is expected to ↑ with time.

- **Focus on HCC surveillance, which may improve outcomes.**

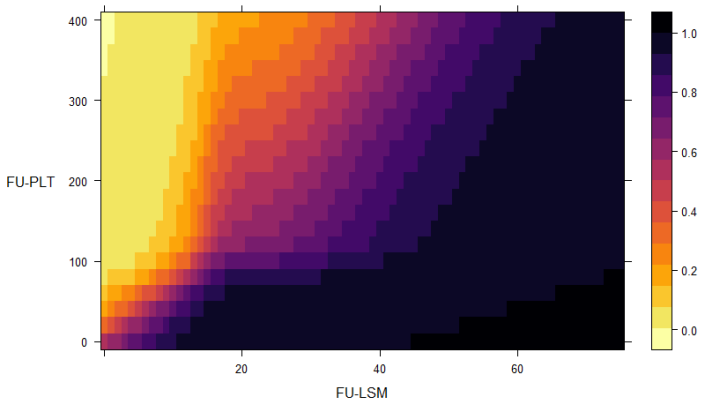
1. Preliminary/unpublished data.

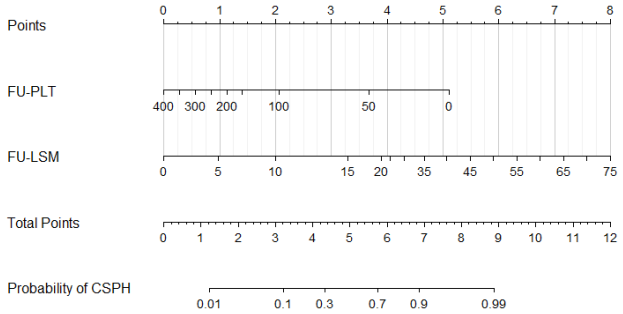
Predictive value for hepatic decompensation (HCC as competing risk)



1. Re-analysis of Semmler et al. Hepatology 2021 and Semmler et al. J Hepatol 2021.

Estimating the probability of CSPH after HCV-cure





- A model based on post-treatment LSM/PLT is provided.
- However, for **clinical practice recommendations**, tools/decision rules have to be **simple** to facilitate their **implementation**.

1. Semmler and Lens et al. J Hepatol 2022

Recommendations #4

- The **Baveno VI criteria** (*i.e.*, **LSM <20 kPa and PLT >150x10^9/L**) can be used to **rule out high-risk varices in patients with HCV- and HBV-induced cACLD** who achieved **SVR and viral suppression**, respectively. **(B.1) (New)**

1. Baveno VII. J Hepatol 2022.

Recommendations #5

- Patients with **cACLD on NSBB therapy with no evident CSPH (LSM <25 kPa) after removal/suppression of the primary aetiological factor**, should be **considered for repeat endoscopy**, preferably after **1–2 years**. In the **absence of varices**, **NSBB therapy can be discontinued**. **(C.2) (New)**

1. Baveno VII. J Hepatol 2022.

Overall, the risk of hepatic decompensation after removal/suppression of the primary aetiological factor is low, particularly if no varices

Decompensation post SVR in HCV compensated cirrhotic patients with clinically significant portal hypertension: too rare for NSBB treatment

NSBB improve decompensation-free survival in viremic HCV compensated cirrhotic patients with clinically significant portal-hypertension (CSPH)

NSBB post SVR in CSPH compensated cirrhotics: still a role in preventing decompensation?

- 148 CPT A, compensated with CSPH
- Never decompensated
- Without high risk varices
- Without additional risk factors for liver disease

- 148 SVR patients
- Median fup: 49 (12-60) months
- 1 decompensation (ascites) concomitant to HCC

Low risk of first decompensation in CSPH patients post SVR: too rare to warrant universal NSBB treatment

Tosetti G et al. *Am J Gastroenterol* 2021. DOI: https://doi.org/10.14309/ajg.0000000000001158

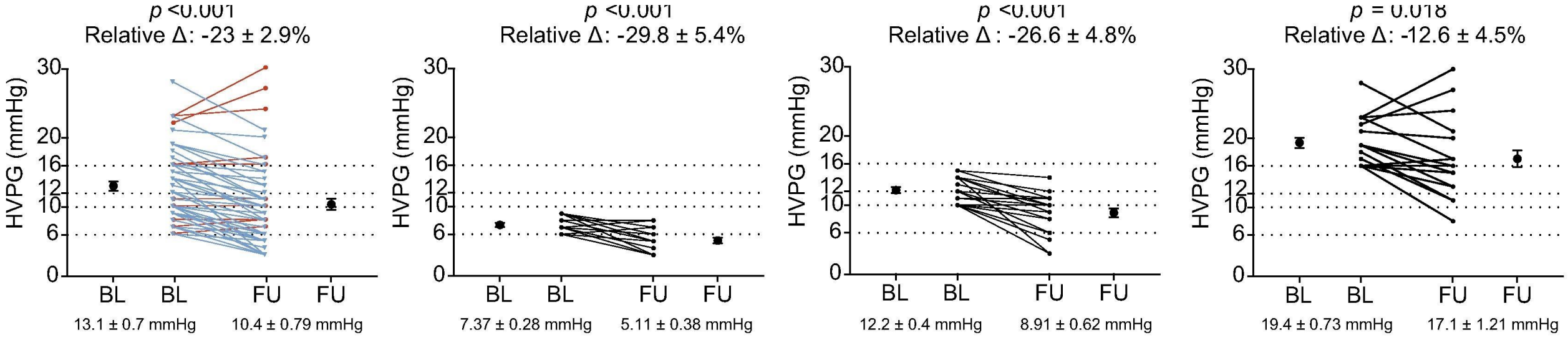
AJG The American Journal of GASTROENTEROLOGY

1. Tosetti et al. Am J Gastroenterol 2021.

Post-treatment LSM & PLT	CSPH/ Varices/ Decompensation	Management
Consistent improvement: LSM < 12kPa & PLT > 150G/L	CSPH excluded (sensitivity: 99.2%) No risk of hepatic decompensation	Discharge from PH surveillance, if no co-factors ! Continue HCC surveillance ! 
LSM < 20kPa & PLT > 150G/L	High-risk varices ruled-out Low prevalence of CSPH Low risk of hepatic decompensation	No need for screening endoscopy 
NSBB-therapy & LSM < 25kPa	Unknown	Repeat endoscopy & discontinue carvedilol (NSBB), if no varices 
NSBB-therapy & LSM ≥ 25kPa	CSPH ruled-in (specificity: 93.6%)	Continue carvedilol (NSBB) treatment 

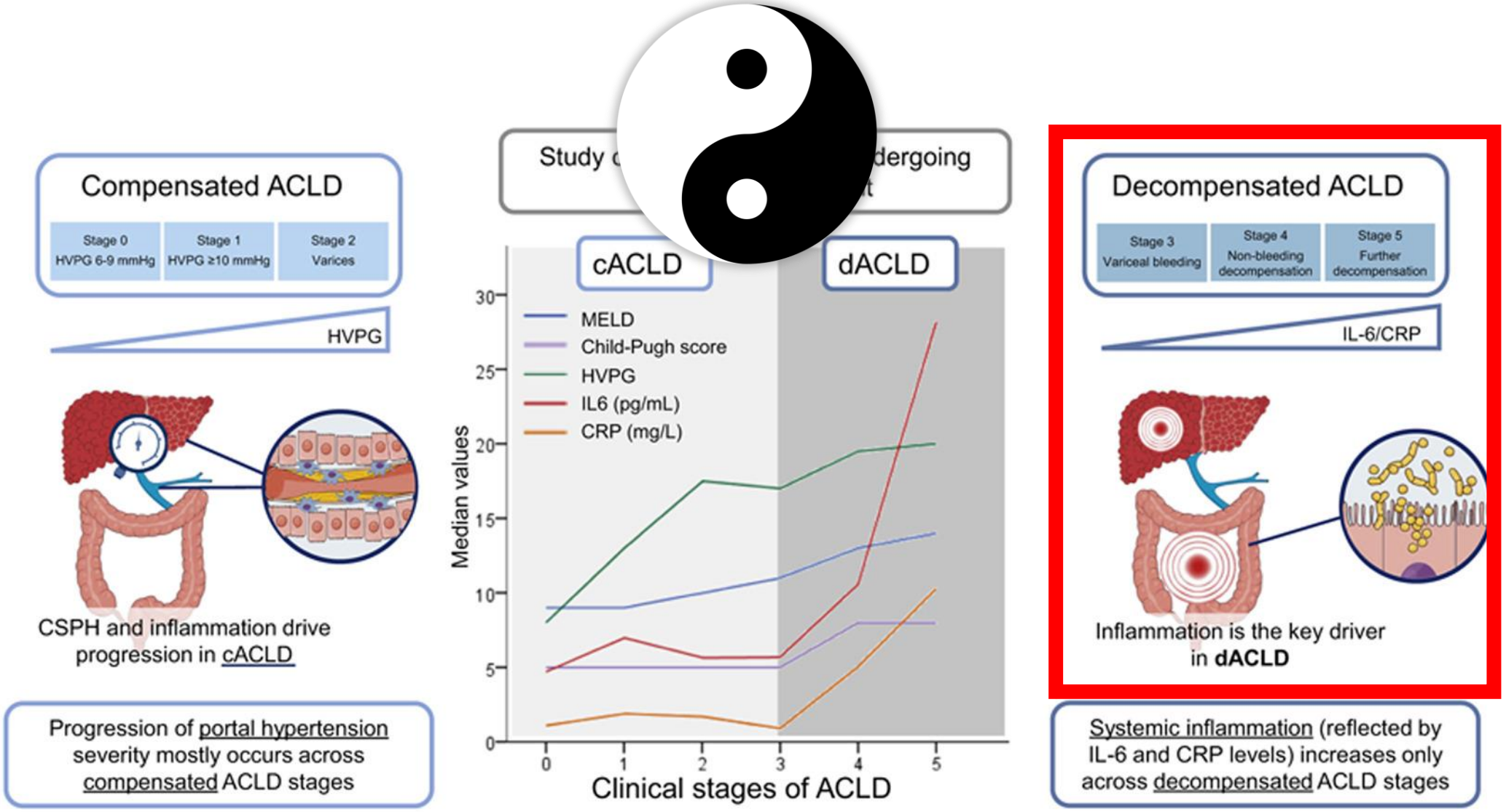
Decompensated cirrhosis

More severe PH – less consistent decreases



Mandorer et al. J Hepatol 2016

Disease-driving mechanisms: cACLD vs. dACLD



Costa and Simbrunner et al. J Hepatol 2021

Recommendations #5

- The concept of **recompensation** implies that there is at least **partial regression of the structural and functional changes of cirrhosis** after removal of the aetiology of cirrhosis. **(A.1) (New)**
- Clinically, the definition of "recompensation" is based on expert consensus and requires **fulfilment of all** the following **criteria**: **(C.2) (New)**
  - Removal of the primary aetiological factor
  - Resolution of ascites (off diuretics), encephalopathy (off lactulose/rifaximin) and absence of recurrent variceal haemorrhage (for at least 12 months);
  - Stable improvement of liver function tests (albumin, INR, bilirubin).

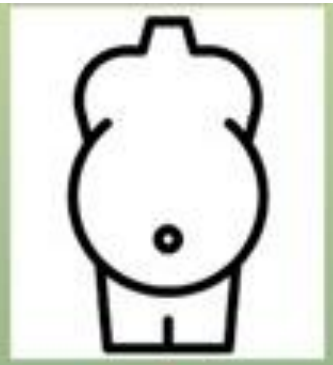
1. Baveno VII. J Hepatol 2022.

Recommendations #5

- Because CSPH may persist despite recompensation, NSBBs should not be discontinued unless CSPH resolves. **(B.1) (New)**
- Resolution of ascites (while on diuretics or after TIPS) and/or lack of recurrent variceal haemorrhage (while on traditional NSBBs + EVL or carvedilol + EVL or after TIPS) without removal/suppression/cure of the primary aetiologic factor and without improvement in liver synthetic function, is not evidence of recompensation. **(B.1) (New)**

1. Baveno VII. J Hepatol 2022.

Impact of aetiological cure



622 patients with cirrhosis and ascites as single first decompensating event

Etiology was cured in 146 patients (23.5%)

Refractory ascites

HR=0.33

Encephalopathy

HR=0.50

HRS-AKI

HR=0.33

HR=0.36

Etiological cure reduced risk of further decompensation (HR 0.46, p=0.001) and ACLF

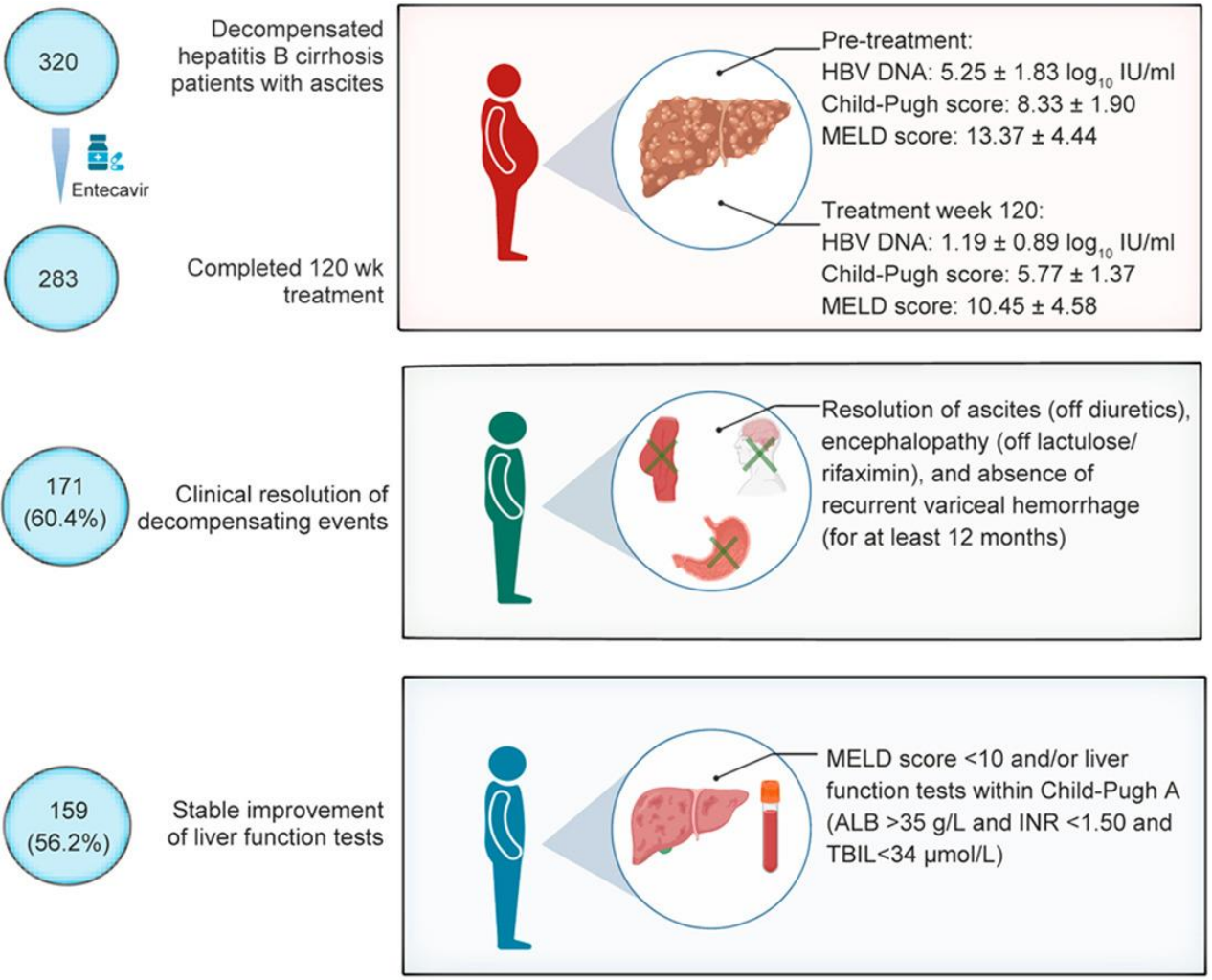
Mortality

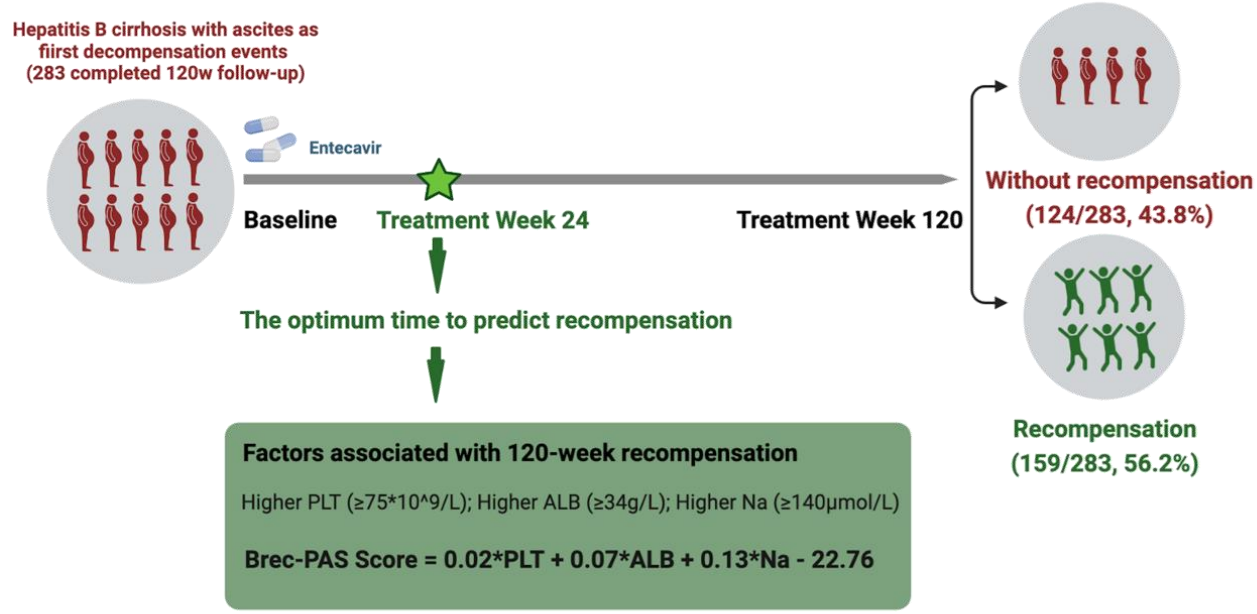
HR=0.35

Etiological cure improved long-term survival (HR 0.35, p<0.001)

Tonon & Balcar et al. Hepatology 2023

Evaluation in HBV infection





Wang & Zao & Deng et al. J Hepatol 2022; Deng et al. EASL Congress 2023 WED-332

Validation in ALD

Decompensated Disease

204 patients with decompensated **alcohol-related cirrhosis** and **alcohol abstinence**

Baseline HVPG measurement

Hepatic Recompensation

18.1%

37 patients achieved recompensation according to Baveno VII criteria

- ✓ Aetiological cure (sustained abstinence)
- ✓ Resolution of ascites & hepatic encephalopathy
- ✓ No bleeding event for >12 months
- ✓ Improvement in liver function

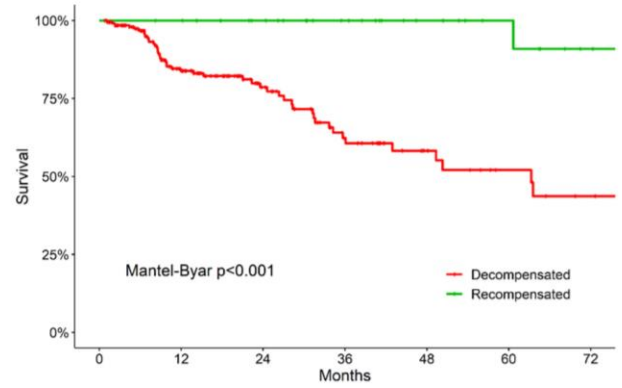
Factors linked to Recompensation:

- ↓ Low Child-Pugh score, HVPG & BMI
- ↑ High albumin & MAP

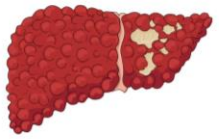
Liver-related mortality

>90% reduced risk upon recompensation

aHR: 0.091 (95%CI: 0.012-0.677); p=0.019



Hepatocellular carcinoma



non-significantly reduced risk of HCC development

HR: 0.398 (95%CI: 0.084-1.878)
p=0.245

Hofer et al. (unpublished)

Take-home messages/*prospects*

- Removal/suppression of the **primary aetiological factor**
  - **SVR** in HCV infection
  - **HBV suppression in the absence of HDV coinfection** in HBV infection
  - **Long-term abstinence from alcohol** in **alcohol-related liver disease**
- **cACLD** after **SVR without co-factors** (generalizibility likely)
  - LSM <12kPa & normal PLT: NO CSPH – 'discharge'/LSM >25kPa: CSPH – carvedilol
- **Recompensation** in 18.1% (ALD)-56.2% (HBV) – **improved prognosis**
  - ***Determinents*** *of recompensation besides disease severity?*
  - ***Clinical implications*** *of recompensation, e.g., delisting, …?*

Thank you for your attention!