"Tratamiento de la hipertensión portal en pacientes con hepatocarcinoma"

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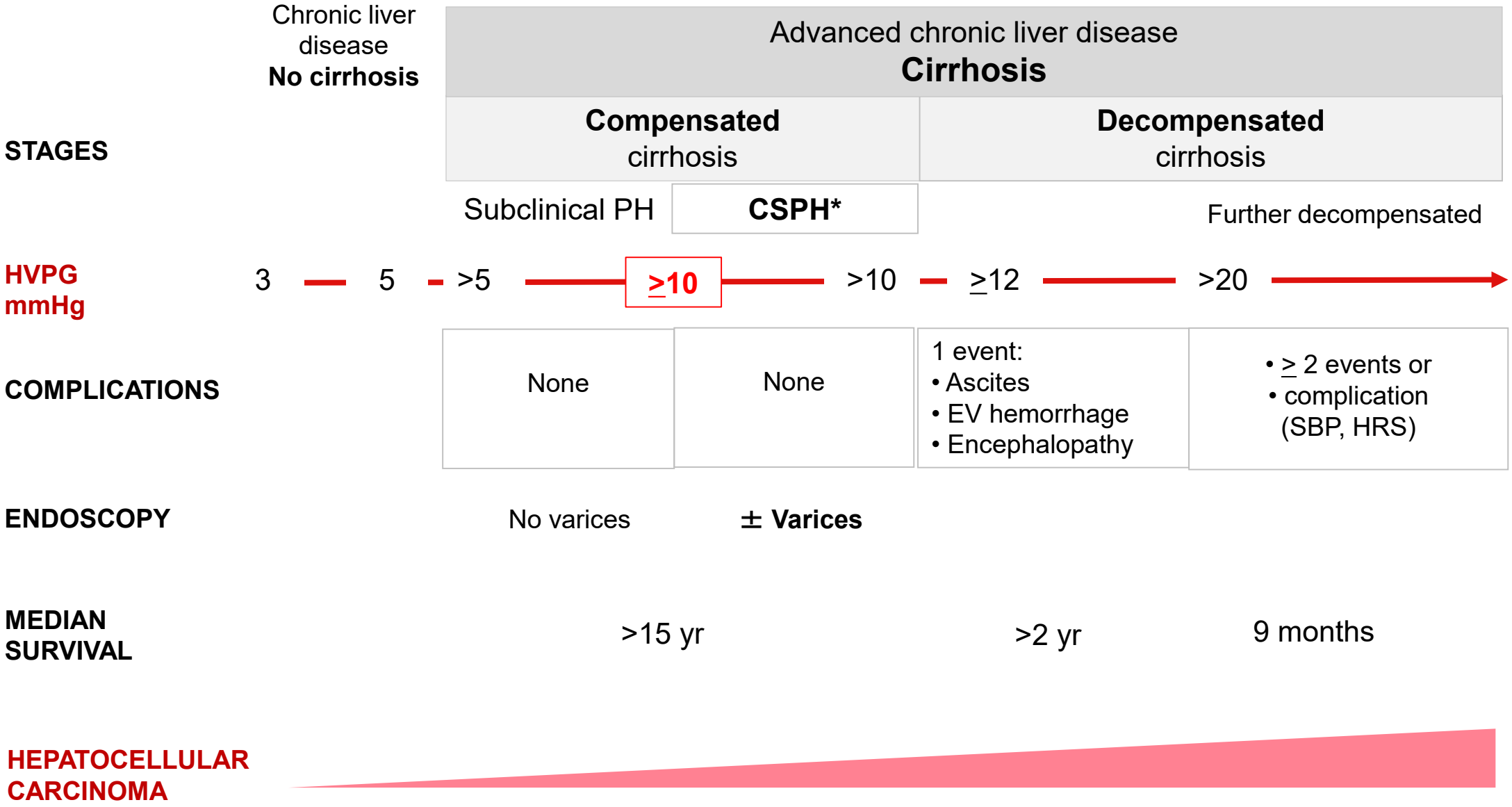
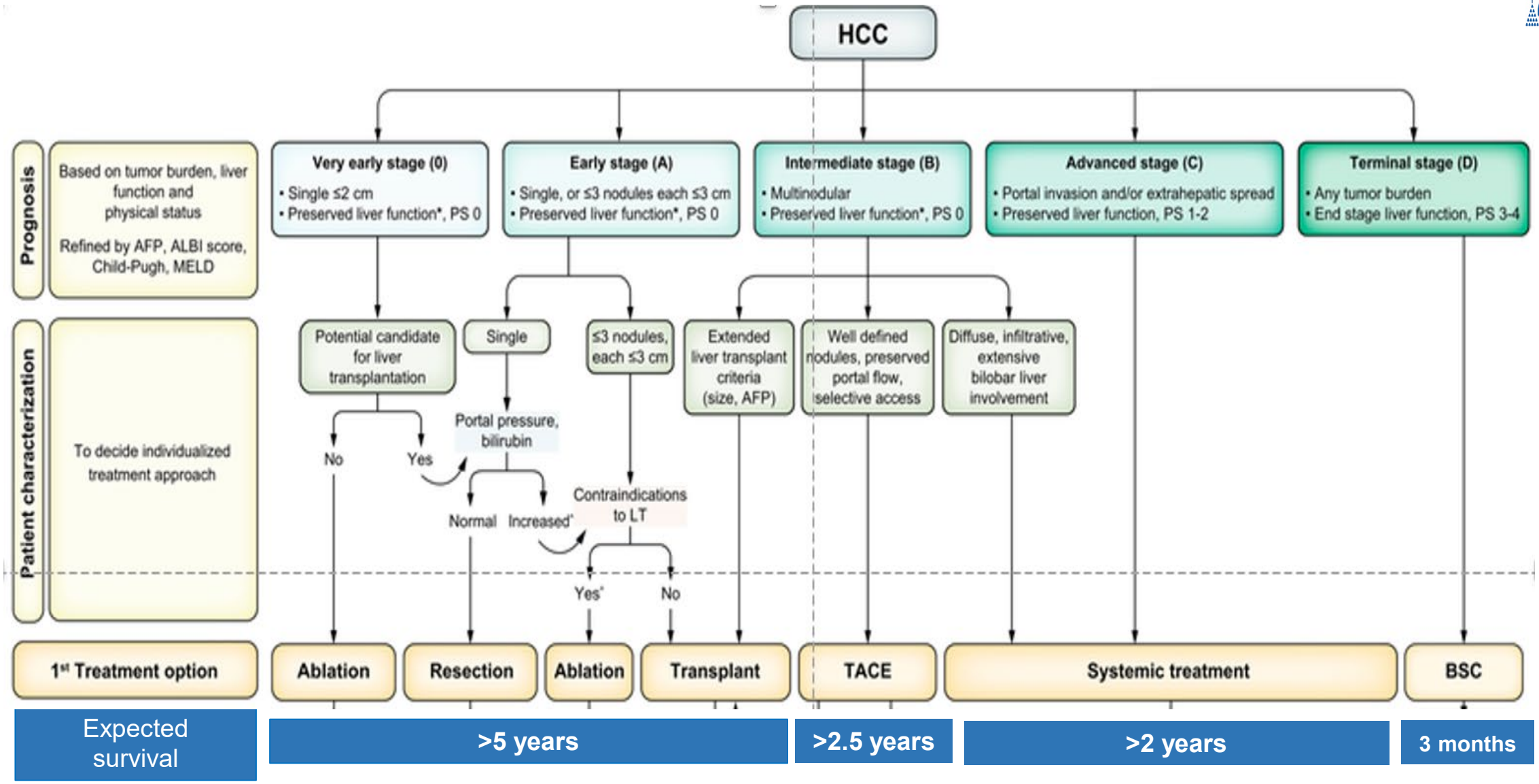
Stages of cirrhosis and hepatocellular carcinoma



Treatment of hepatocellular carcinoma in cirrhosis



Agenda

Cirrosis y hepatocarcinoma

— CSPH: relevancia y diagnóstico

— Profilaxis de la hemorragia (y la descompensación)

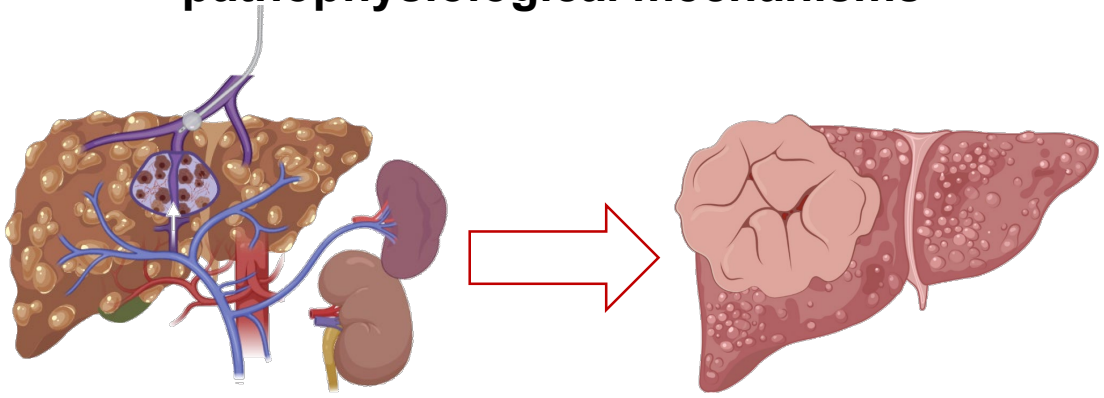
— Terapia sistémica y hemorragia por varices

— Trombosis venosa portal

— Importancia del tratamiento de la cirrosis

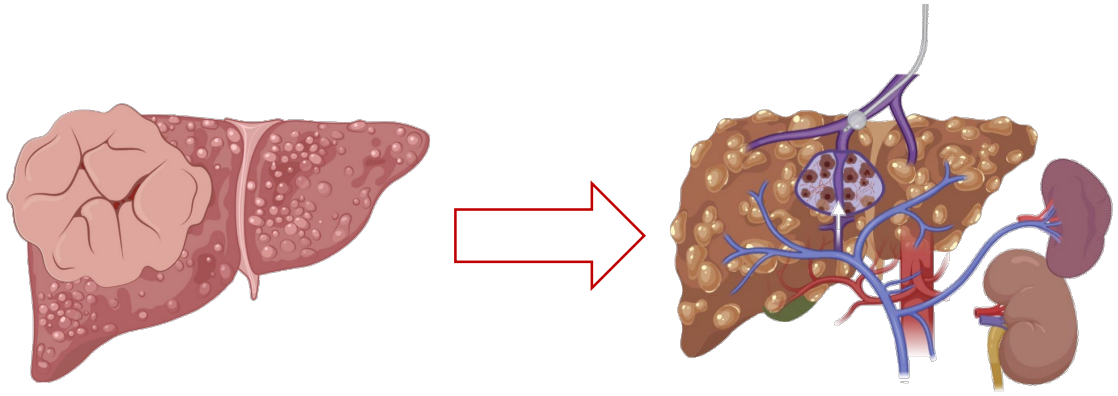
Bidirectional relationship between cirrhosis and hepatocellular carcinoma

Cirrhosis and HCC share pathophysiological mechanisms



- Chronic inflammation
- Immunosuppressive and hypoxic environment
- Angiogenesis (↑ VEGF, ↑ PDGF)

HCC worsens portal hypertension

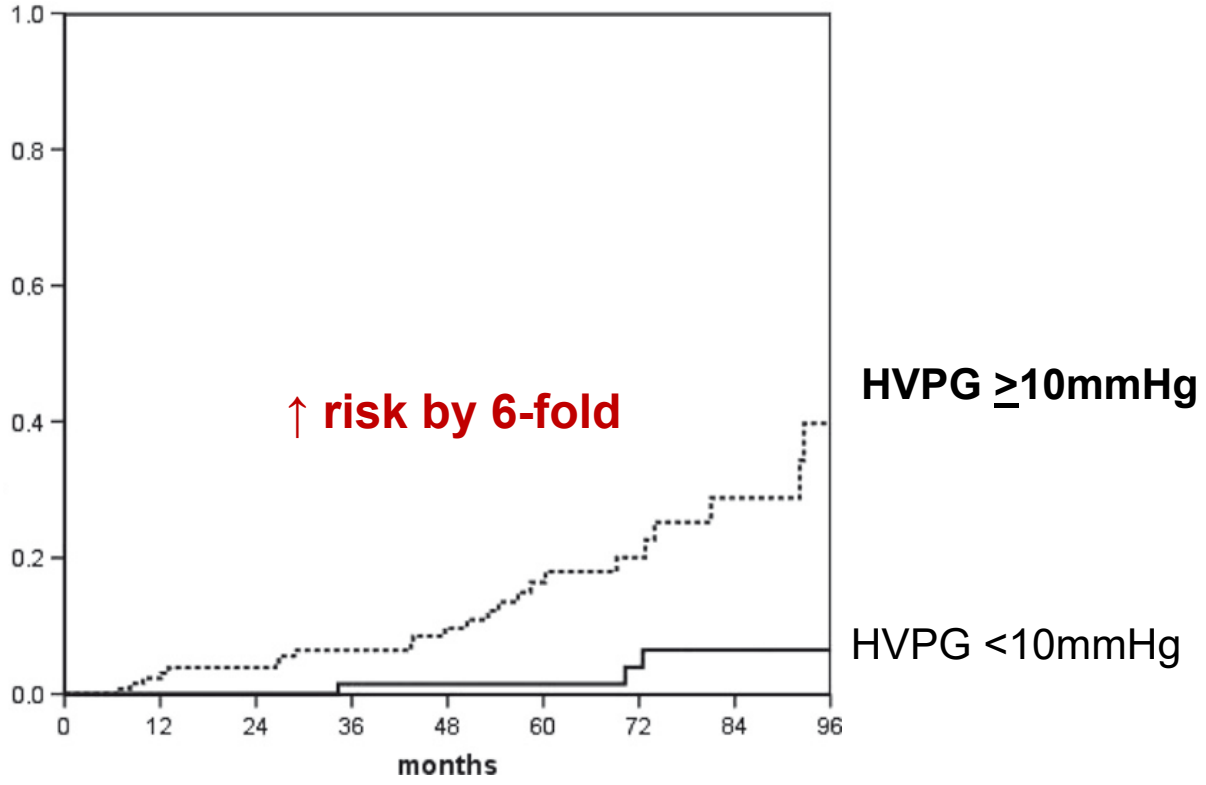


- Arteriovenous shunting
- Modifications of liver architecture
- Tumoral invasion of the portal vein

Presence of CSPH is associated with increased HCC development

213 patients Child-Pugh A, 62% HCV
HCC 12.2% during a f-up of 58 months

Incidence of hepatocellular carcinoma



C Ripoll et al. JHEP 2009

Meaning and diagnosis of clinically significant portal hypertension

Definition: HVPG ≥10 mmHg

Meaning:
- at risk of clinical decompensation
- ↑ splanchnic blood flow contributes to portal hypertension
- low-grade systemic inflammation
- at greater risk of HCC

Diagnosis:

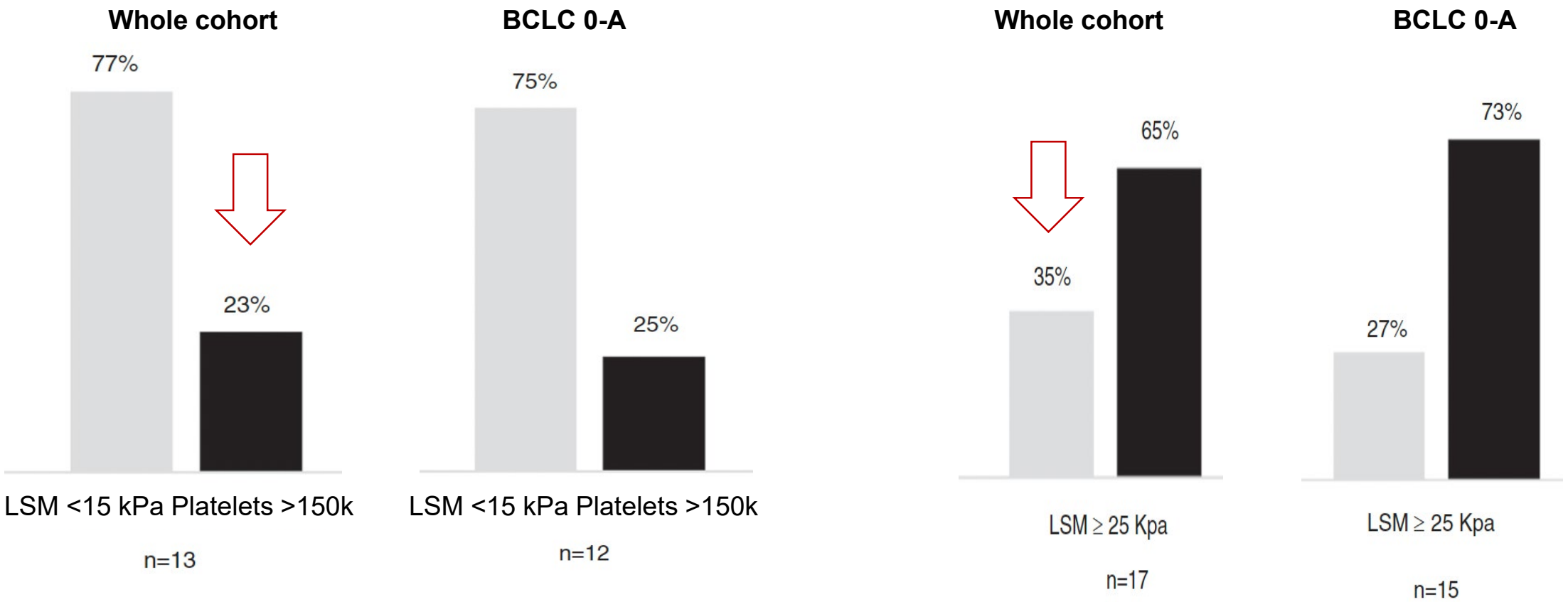
- Gastro/esophageal varices (endoscopy, CT)
- Portosystemic collateral vessels (US, CT)
- **Rule of 5:** transient elastography and platelets

R De Franchis et al. Baveno VII. JHEP 2022

Inaccuracy of the Baveno VII "rule of 5" to identify CSPH in patients with HCC

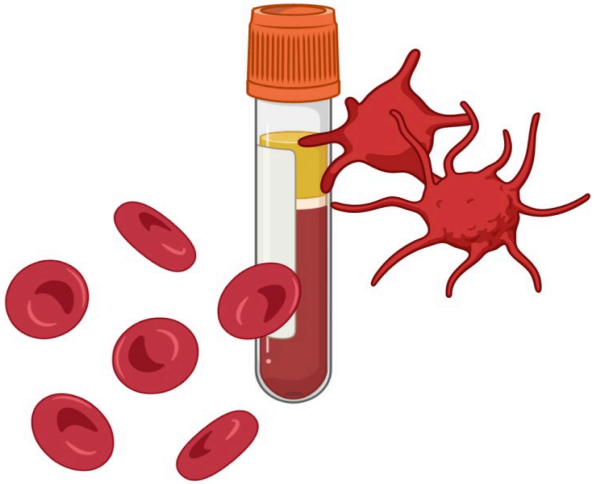
~25% with "**favourable** Baveno VII" criteria have CSPH

~35% with "**unfavourable** Baveno VII" criteria do not have CSPH



M Allaire et al. APT 2023

Potenciales inconvenientes para aplicar la “regla del 5” en pacientes con cirrosis y hepatocarcinoma

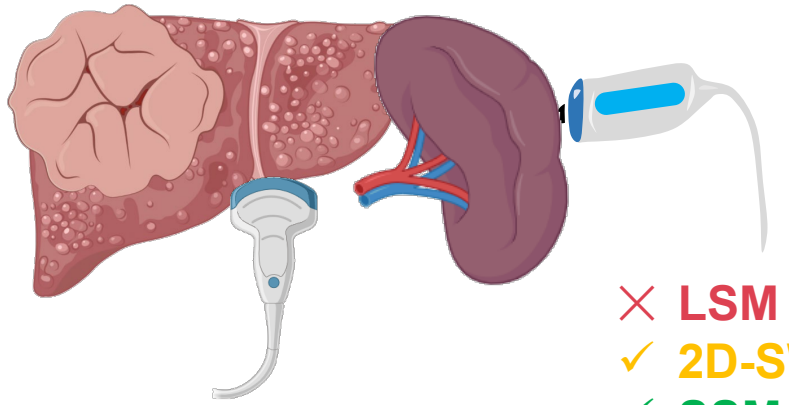


Plaquetas

Infraestima HPCS

Trombocitosis reactiva a proceso tumoral

Menor precisión diagnóstica



Rigidez hepática medida por ET Fibroscan ©:

Sobrestima HPCS

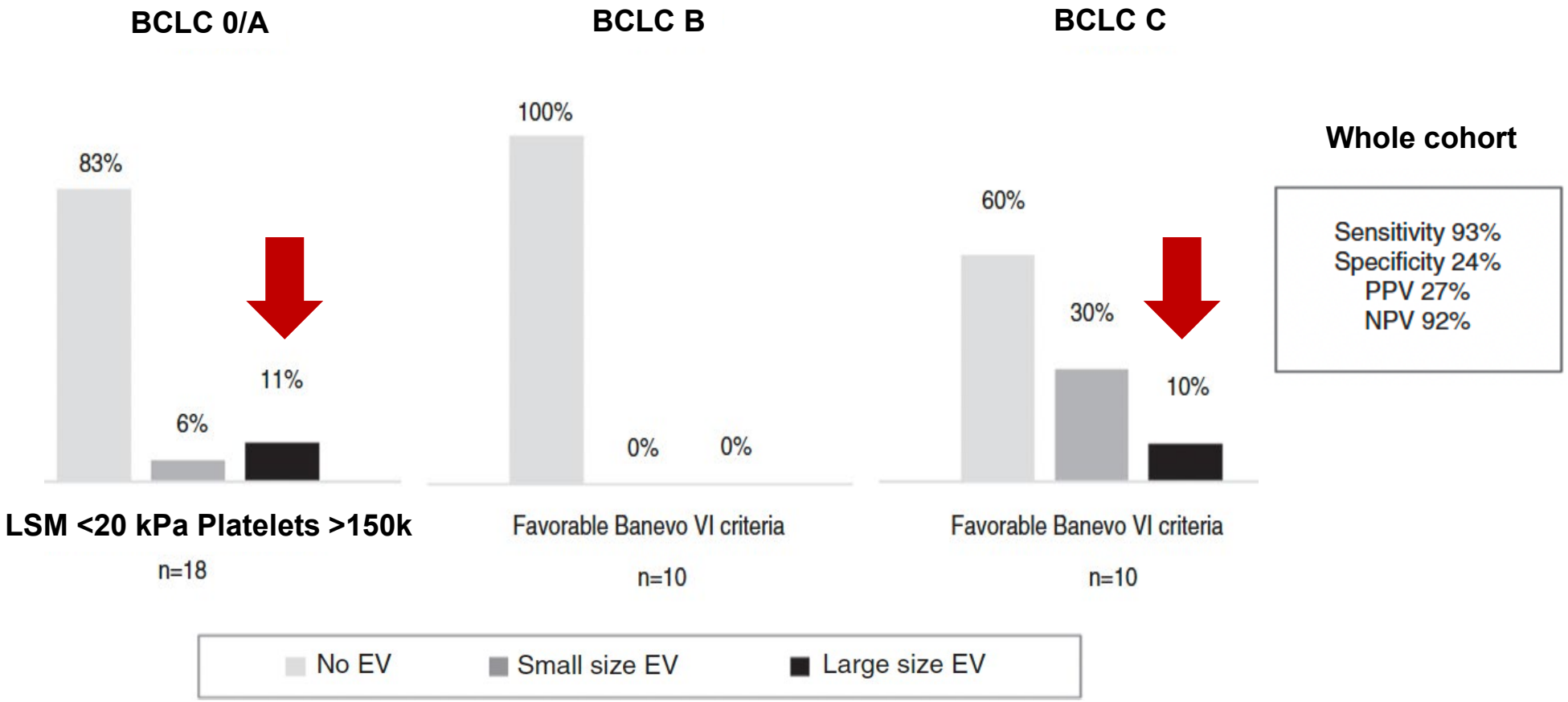
Tejido tumoral interpuesto

Menor precisión diagnóstica

Cortesía Dr Guerrero

Inaccuracy of the Baveno VI criteria to "rule out" large EV in patients with HCC

~10% with "**favourable** Baveno VI" criteria have large EV

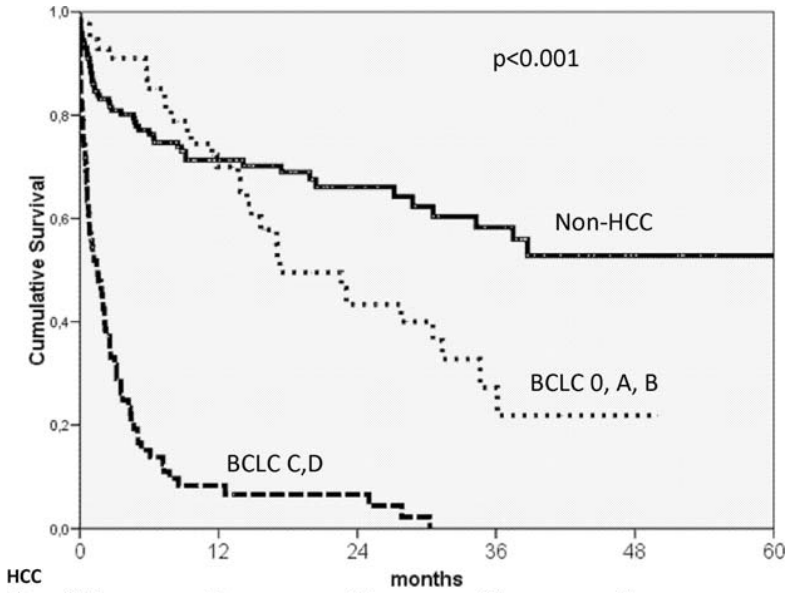


M Allaire et al. APT 2023

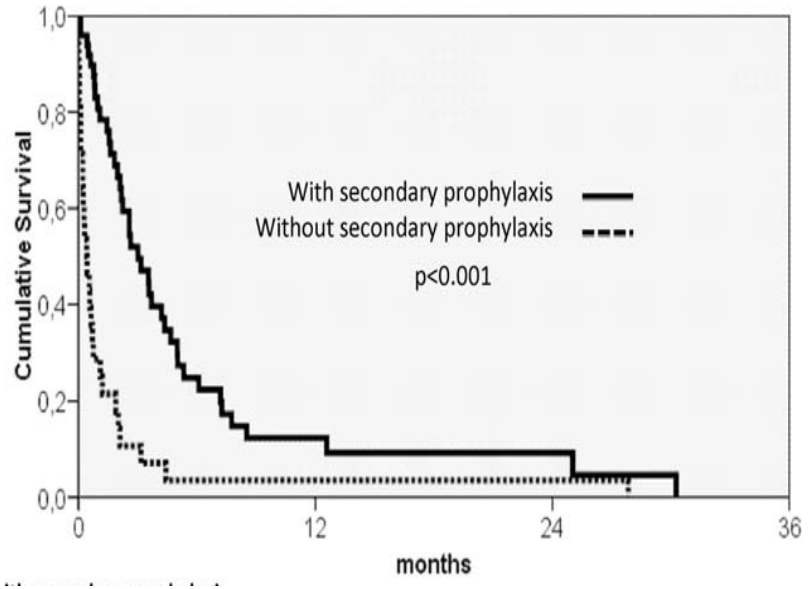
Prevention of variceal rebleeding impoves outcomes in patients with HCC

292 patients, 146 with HCC, after variceal bleeding

Increased mortality in HCC patients after variceal bleeding



Rebleeding prophylaxis lowers mortality



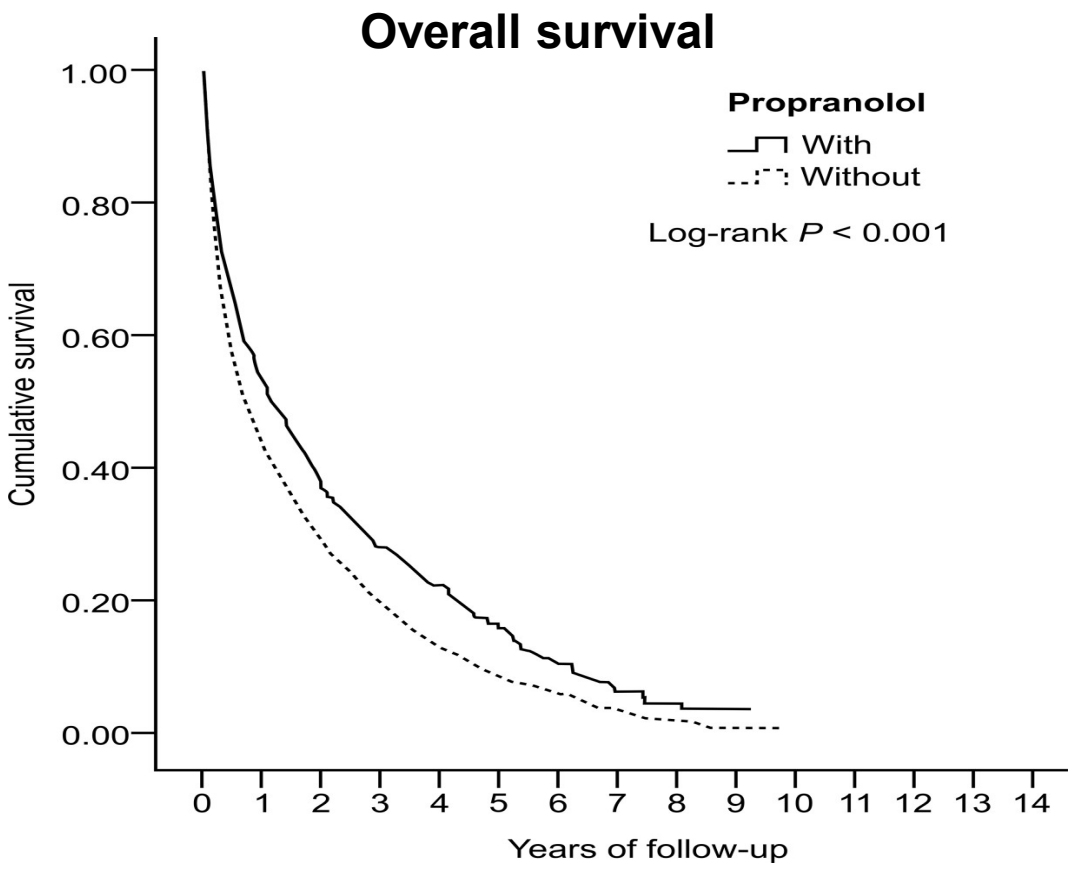
Predictors of death

Variable	95% CI
BCLC classification	4.04 (2.24-7.27)
Lack of secondary prophylaxis	4.00 (2.27-6.67)
Child-Pugh score	1.29 (1.15-1.44)
PVT	
None (reference)	–
Benign	0.90 (0.42-1.96)
Malignant	2.16 (1.27-3.68)

C Ripoll et al. Hepatology 2013

Propranolol improves survival in patients with cirrhosis and advanced HCC

Retrospective cohort January 2000 and December 2013
Unresectable/metastatic HCC, 1560/3120 propranolol/non-prop
1:2 propensity score in both cohorts

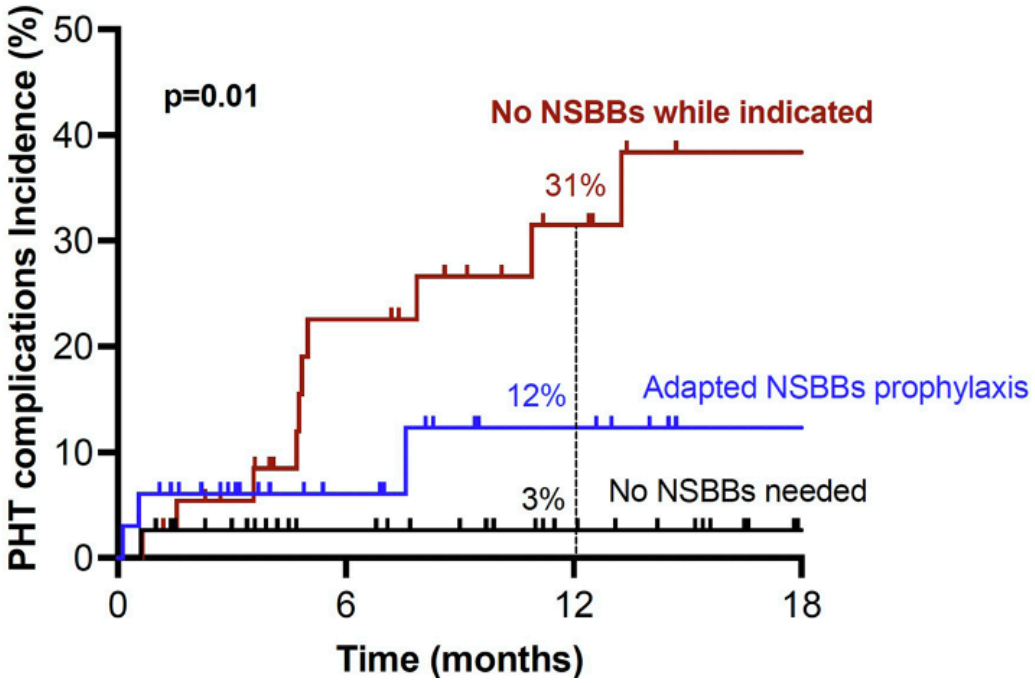


PY Chang et al. PLOsONe 2019

Propranolol improves outcomes in patients with cirrhosis and HCC treated with TACE

109 patients with HCC treated with TACE, 2013-2023

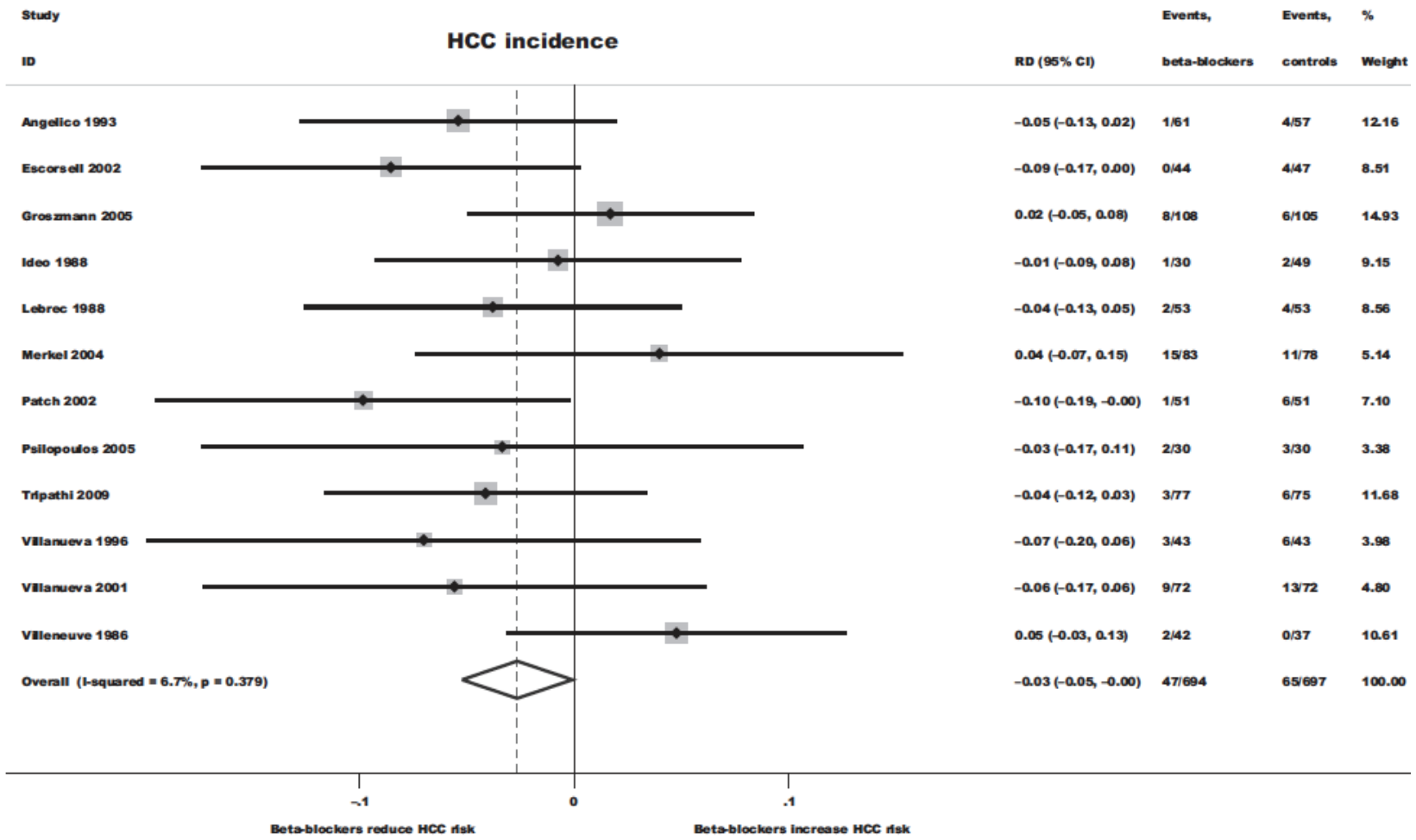
Complications of portal hypertension



Risk factors associated with complications of portal hypertension	(HR, CI)	
• History of EH	55.3	7.4-413
• No NSBB when indicated	4.16	1.4-11.8

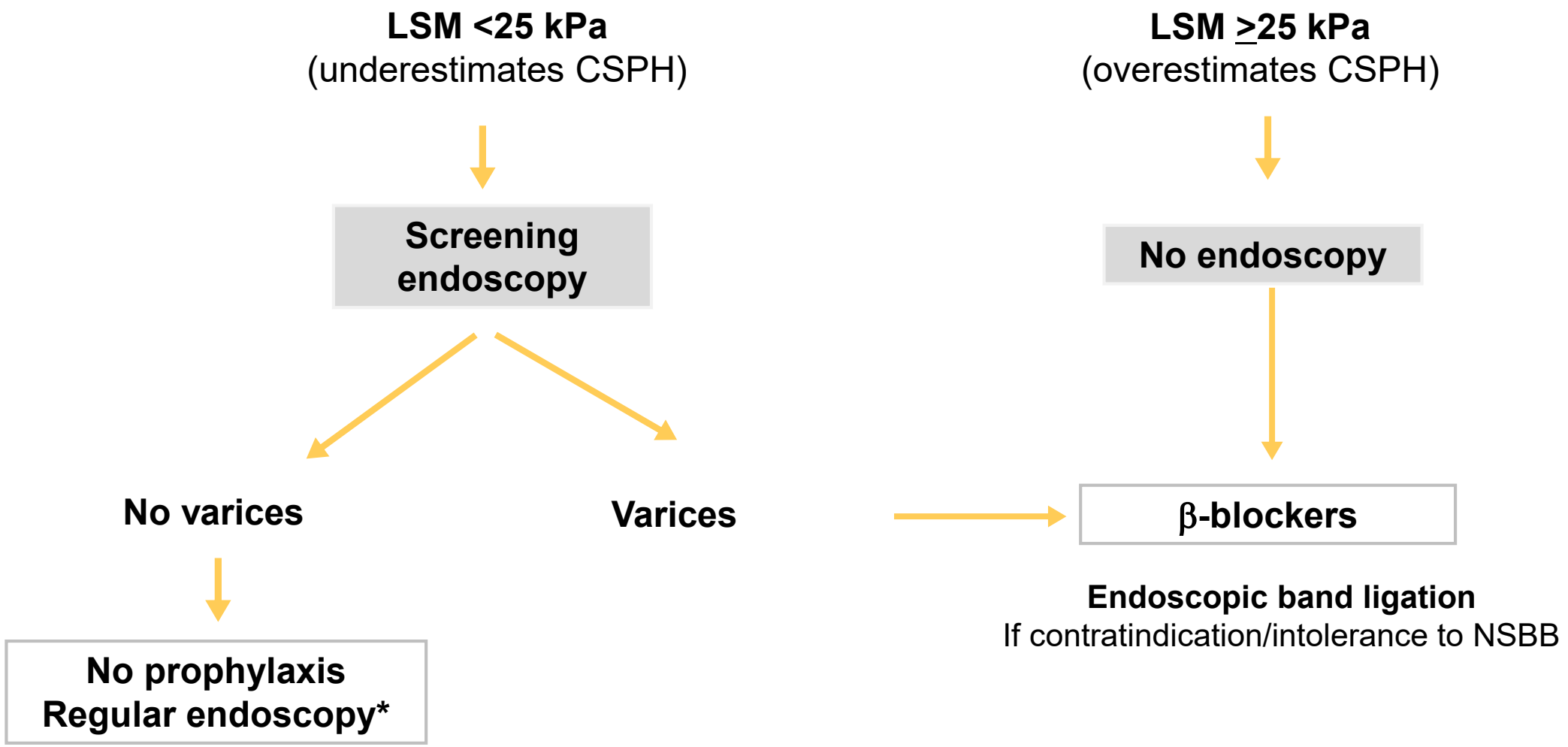
M Allaire et al. Clin Res GH 2025

NSBB may decrease the incidence of HCC in patients with cirrhosis



Thiele M, et al. Liver Int. 2015

Prevention of first variceal bleeding/decompensation in patients with cirrhosis and HCC



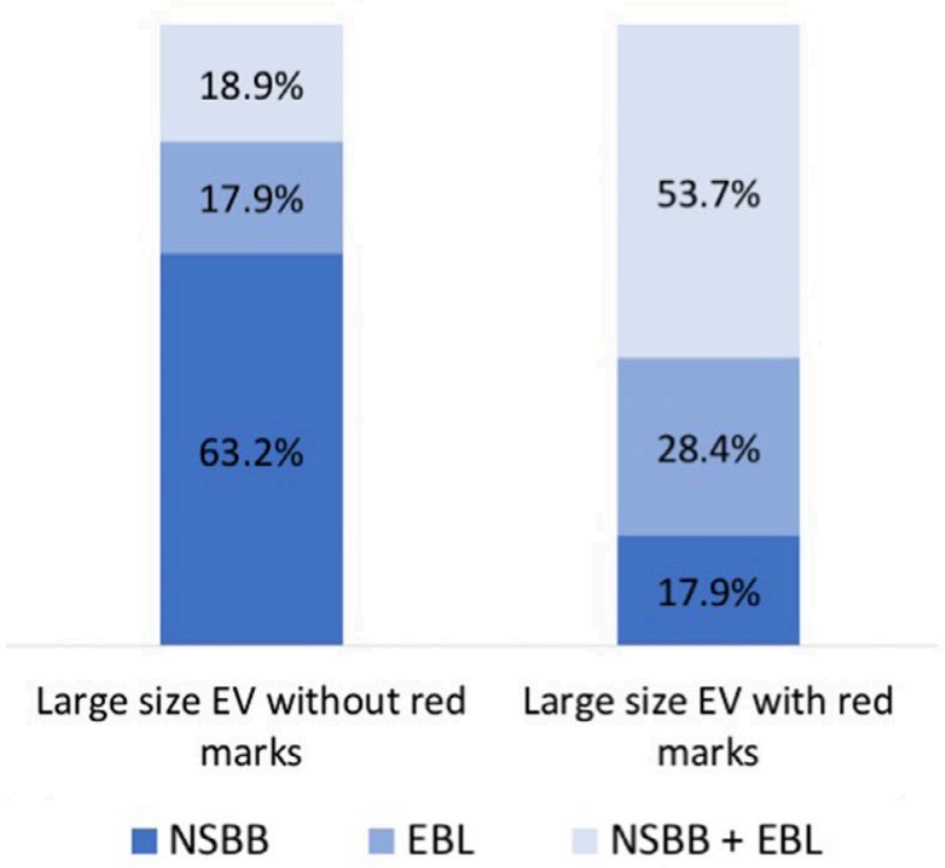
* Every 1-2 years and
in case of HCC progression and portal invasion

Expert opinion
D Thabut et al. JHEP 23

Primary prophylaxis in patients with cirrhosis and HCC on systemic therapy

French survey: Hepatologists and Oncologists

Primary prophylaxis



	Hepatologists	Oncologists
Large varices		
NSBBs	73%	57%
EBL	15%	20%
NSBBs + EBL	11%	23%
Large varices + red wale marks		
NSBBs	17%	20%
EBL	30%	25%
NSBBs + EBL	53%	54%

Overuse of combined therapies
(out of current recommendations)

Allaire M et al. Clin Res Hepatol Gastroenterol. 2023

Prevention of rebleeding/further decompensation **in patients with cirrhosis and HCC**

Variceal bleeding

NSBB+EVL

TIPS

End-point: variceal bleeding

R De Franchis et al. Baveno VII. JHEP 2022
Personal

Agenda

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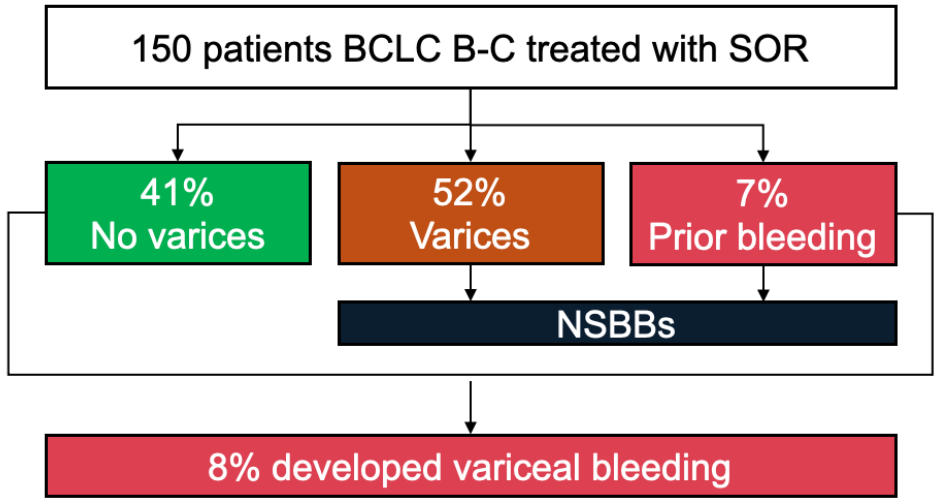
Acute variceal bleeding in patients with advanced HCC on trials of systemic therapy

Author	Study	Exclusion criteria	PH-related bleeding
Llovet et al, NEJM 2008	**SHARP** Sorafenib (n=299) vs Placebo (n=203)	Variceal bleeding 30 days before randomization	**Sorabenib: 2.6%** Placebo: 3.4%
Kudo et al, Lancet 2018	REFLECT Sorafenib (n=476) vs Lenvatinib (n=478)	Variceal bleeding or EBL 28 days before randomization	Sorafenib: 1.0% Lenvatinib: 1.4%
Finn et al, JCO, 2020	KEYNOTE Pembrolizumab (n=279) vs Placebo (n=134)	Variceal bleeding 6 months before randomization	Pembrolizumab: 1.1% Placebo: 0.7%
Yau et al, Ann Oncol 2020	CHECKMATE Nivolumab (n=371) vs Sorafenib (n=134)		Nivolumab: 1.9% Sorafenib: 0.4%
Abouth Alfa et al. NEJM 2022	**HYMALAYA** Treme-Durva (n=393) vs Sorafenib (n=389)	Portal vein thrombosis Variceal bleeding 12 months	**Treme-Durva: 0%** Sorafenib: 0%
Finn et al, NEJEM 2020	**IMBRAVE** Atezo-Beva (n=336) vs Sorafenib (n=165)	Variceal bleeding 6 months before randomization	**Atezo-Beva: 2.6%** Sorafenib: 0.4%

Courtesy of A. Guerrero

Risk of variceal bleeding in patients with advanced HCC on sorafenib

Real-world observational cohort, 2008-2013



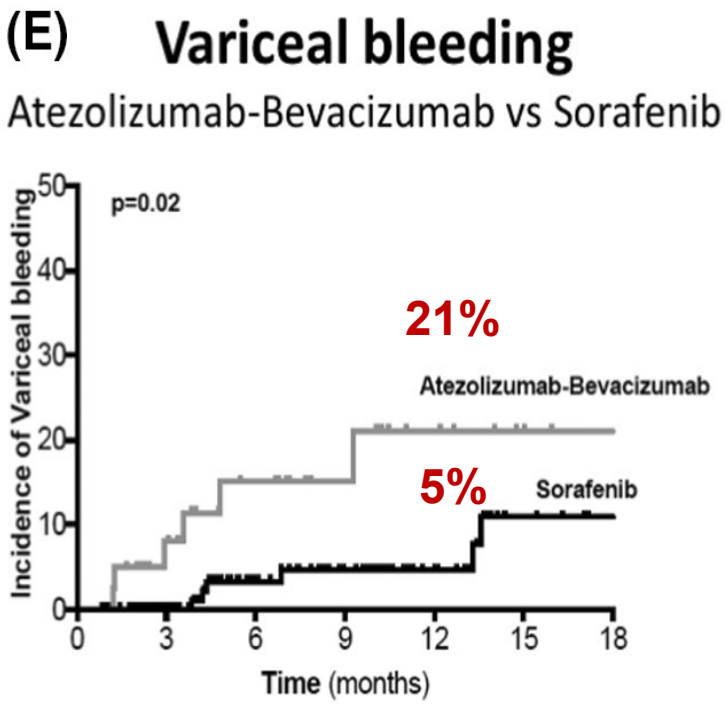
Risk factors of acute variceal bleeding (HR, CI)

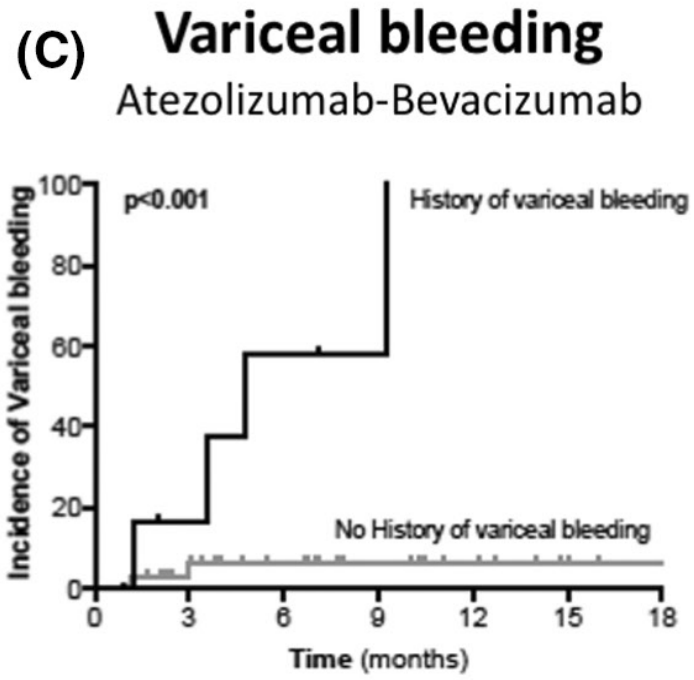
Predictor (code)	HR (95% CI)	*p* value
Bilirubin >1.0 mg/dl (yes vs. no)	2.79 (057–13.58)	0.202
Albumin >4.0 mg/dl (yes vs. no)	0.11 (0.14–0.92)	0.04
Neoplastic PVT (yes vs. no)	15.82 (1.9–131.28)	0.01
Medium/large EVs (yes vs. no)	1.99 (0.92–4.32)	0.08
Previously treated EVs (yes vs. no)	1.88 (0.88–4.04)	0.10

M Lavarone et al. UEG Journal 2016

Risk of variceal bleeding in patients with advanced HCC on systemic therapy

43 patients treated with atezolizumab–bevacizumab since 2020
122 patients treated with sorafenib between 2013 - 2022





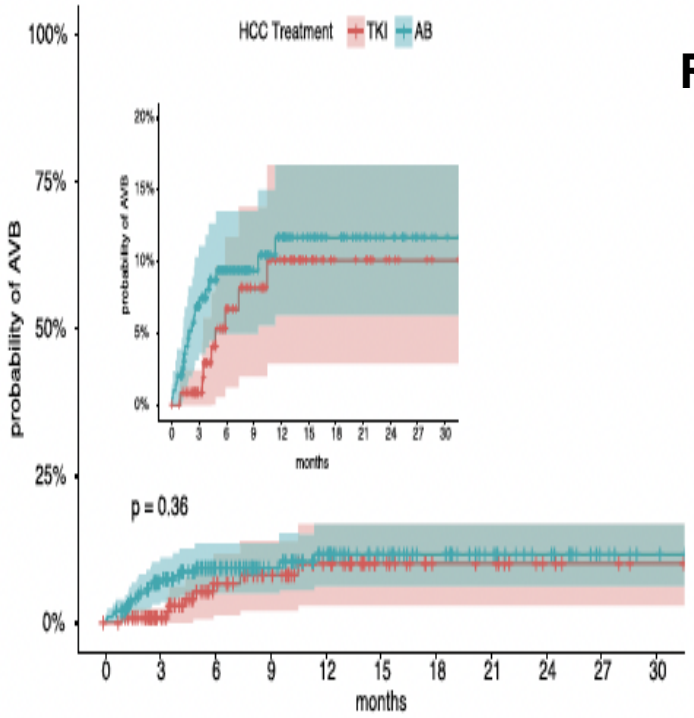
Factors associated with AVB (HR, CI)

• History of variceal bleeding	10.58	1.26-88.7
• History of ascites	1.6	0.19-13.28

E Larrey, et al. Liver Int. 2022

Risk factors of acute variceal bleeding in patients with advanced HCC on systemic therapy

200 patients treated with atezolizumab–bevacizumab since 2020
122 patients treated with sorafenib between 2013 - 2022



Risk factors of acute variceal bleeding, Cox model

Variable	Atezolizumab-Bevacizumab Multivariate analysis HR (95% CI)	*p*-value
Presence of EV	**3.22 (1.02–10.14)**	**0.04**
PVTT	**3.25 (1.16–9.07)**	**0.02**
History of AVB < 6 months	**4.32 (1.17–15.92)**	**0.03**
History of AVB ≥ 6 months	1.68 (0.37–7.52)	0.5

Not associated with AVB:
- Therapeutic AG (20%)

~25% of patients did not receive NSBB

D Thabut et al. Dig Dis Sci 2024

Hemorragias por hipertensión portal en ensayos fase 3 de tratamiento sistémico en hepatocarcinoma en estadio avanzado

DIGESTIVO RAMON Y CAJAL MADRID
Universidad de Alcalá

¿poblaciones representadas?

IMbrave 150 **Hemorragia variceal** Atezo-Beva (2.6%) vs. SOR (0.4%)		**HIMALAYA** **Hemorragia variceal** Trem-Durva (0%) vs. SOR (0%)
Endoscopia previa obligatoria Varices no tratadas excluidas HDA < 6 meses excluidos Varices 26% Varices requieren tto 11%	Laxitud inclusión / Seguridad	Endoscopia previa no necesaria HDA < 12 meses excluidos No datos sobre estado de varices
Población “alto riesgo” **incluida** Trombosis tumoral porta principal Infiltración hepática >50% Invasión vía biliar		Población “alto riesgo” **excluida** Trombosis tumoral porta principal

Cortesía de A Guerrero

Considerations of variceal bleeding prophylaxis in patients with advanced HCC on systemic therapy

Screening endoscopy mandatory!!!
Prophylaxis of variceal bleeding mandatory!!

Presence of varices
• Atezo-Beva not contraindicated

History of variceal bleeding
• Treme-Durva preferred

Tumoral PVT
• Represented in IMBRAVE
• Treme-Durva preferred if previous variceal bleeding

Variceal bleeding while on Atezo-Beva
• Standard treatment
• Choices?:
Atezo mono vs. Durva-Treme / TKIs vs. TIPS+Atezo-Beva

Thabut D, Kudo M. J. Hepatol 2022. Allaire M, et al. Hepatology 2024. Singal AG, et al. Hepatology 2023

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— CSPH: relevancia y diagnóstico

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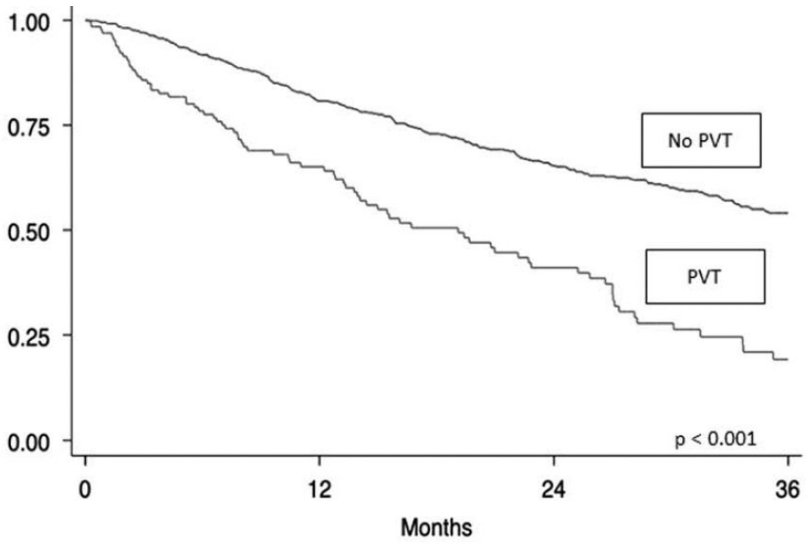
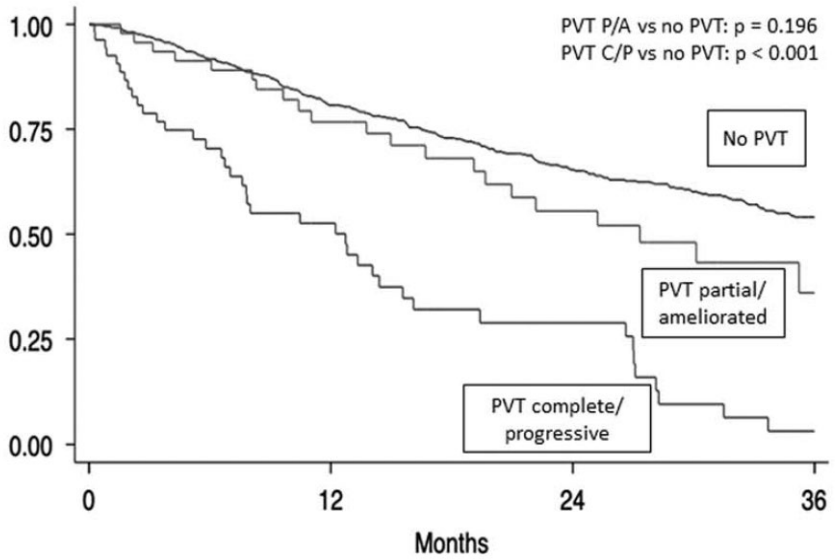
Progresive and occlusive non-tumoral PVT worsen survival in patients with cirrhosis and HCC

750 patients with HCC treated with ablation of HCC
88 PVT, 662 w/o PVT at baseline
71% Child A and low baseline tumoral burden
F-up 36 months

Survival according to the presence of PVT



Survival according to the evolution



Risk factors of PVT at HCC diagnosis:
- Pretreatment total tumor volume (p < 0.001)
- CSPH (p = 0.005)

71% Child A and low baseline tumoral burden

Risk factors of complete/progressive pattern in non-AG:
- Non-response to HCC treatment (p < 0.01)

Child A vs. B/C (NS)

M Senzolo et al. Hepatology 2023

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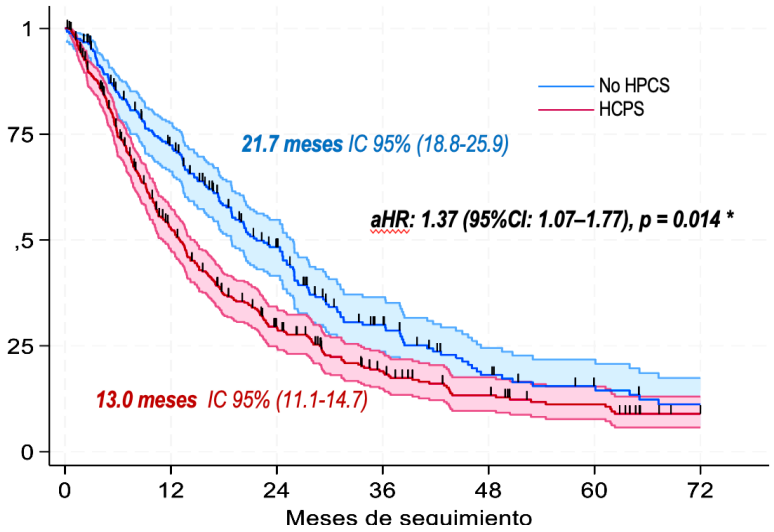
Presence of CSPH worsens the prognosis of patients compensated cirrhosis and advanced HCC on systemic therapy

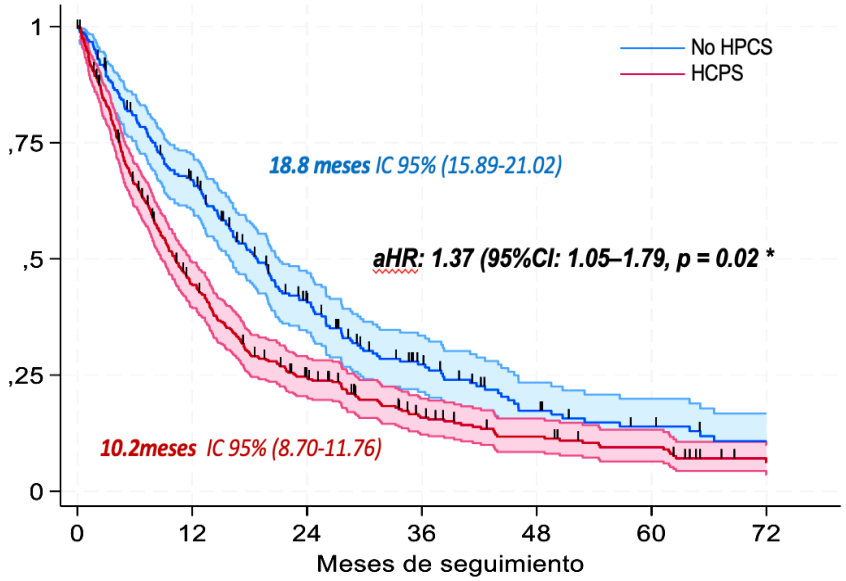
649 patients with compensated cirrhosis and
advanced HCC treated with systemic therapy
ITK 91%, Atezo-Beva 8%
F-up 14.6 months

Overall survival



Mediana de seguimiento: 14.6 meses (7.4-26.0)

Therapeutic window



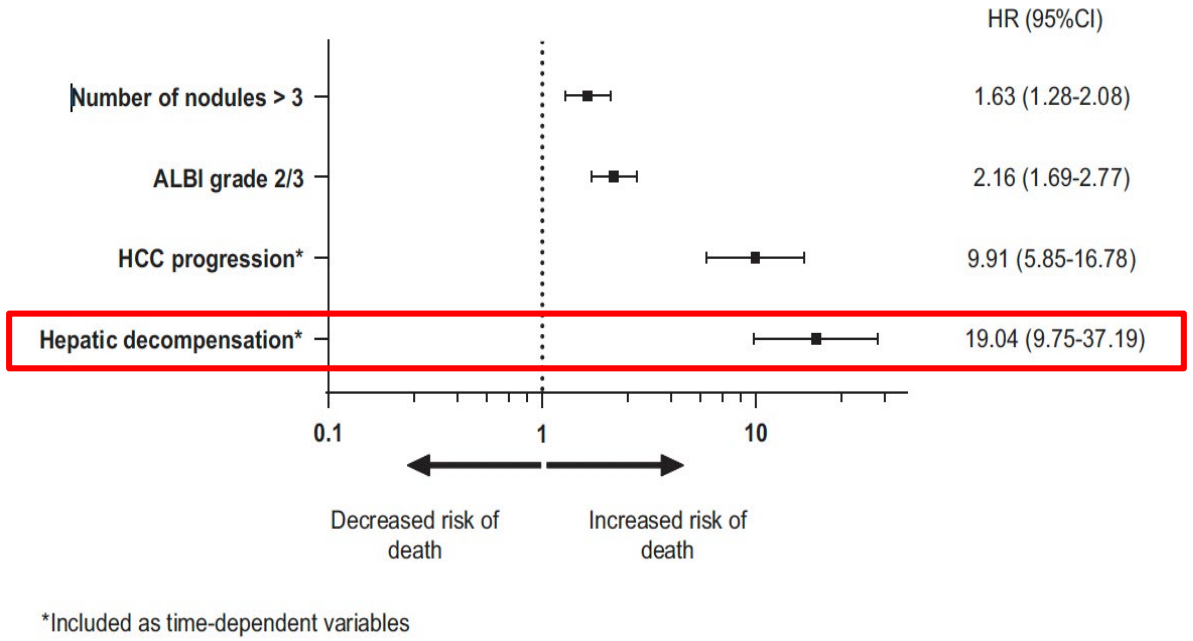
* Ajustado por edad, etiología, MELD, ALBI, estadio BCLC, tipo de tratamiento sistémico

A Guerrero et al. EASL 2025

Hepatic decompensation as the major driver of mortality in patients with HCC treated with atezo-beva

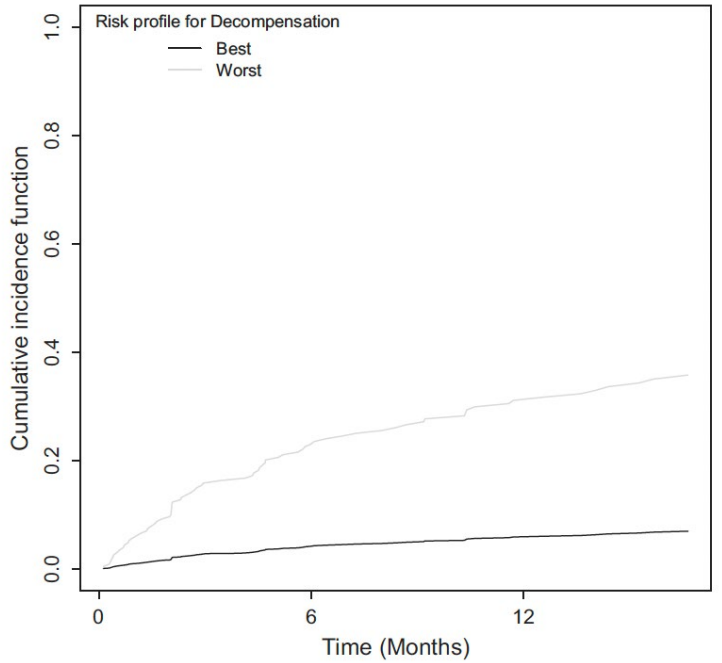
571 patients with compensated cirrhosis and
advanced HCC treated with Atezo-Beva
51% tumoral progression, 16.5% decompensation
F-up 11 months

Predictors of death



*Included as time-dependent variables

Probability of decompensation



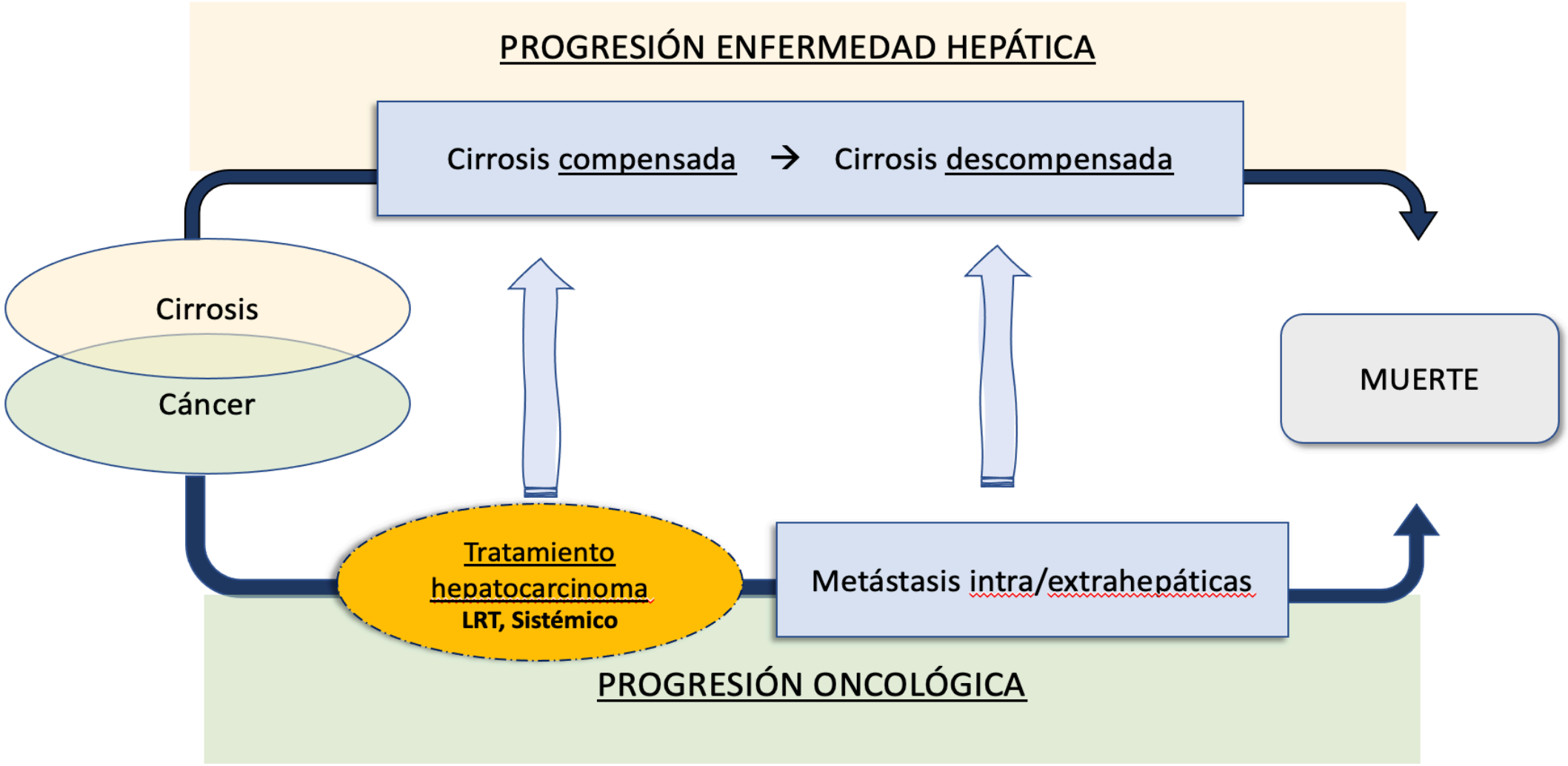
ALBI 1

Treated viral etiology

No evidence of tumor progression in 50% of decompensations

C Celso et al. Hepatology 2024

La reserva funcional hepática y la progresión tumoral compiten en el riesgo de muerte en pacientes con cirrosis y HCC



Cortesía de A Guerrero