Natural history of decompensation

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UIMH

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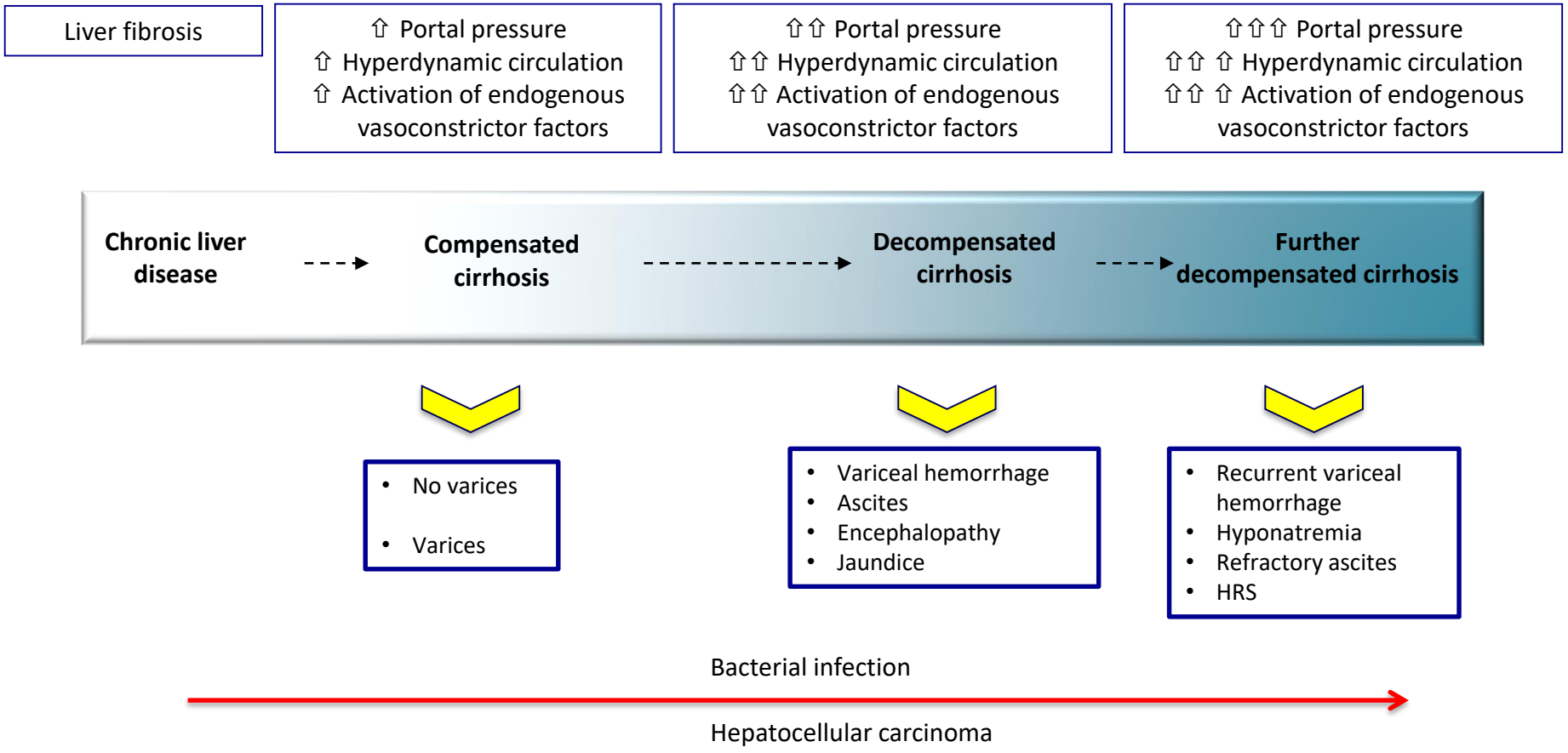
Disclosures

- 2016-2023: Biovie; Advisory Board, Patent
- 2014-2022: CSL Bhering; Speaker invitation and travel grant
- 2018-2022: Grifols; Speaker invitation and travel grant
- 2022-2023: Kedrion; Speaker invitation
- 2021-2023: Biomarin ; Advisory Board

Agenda

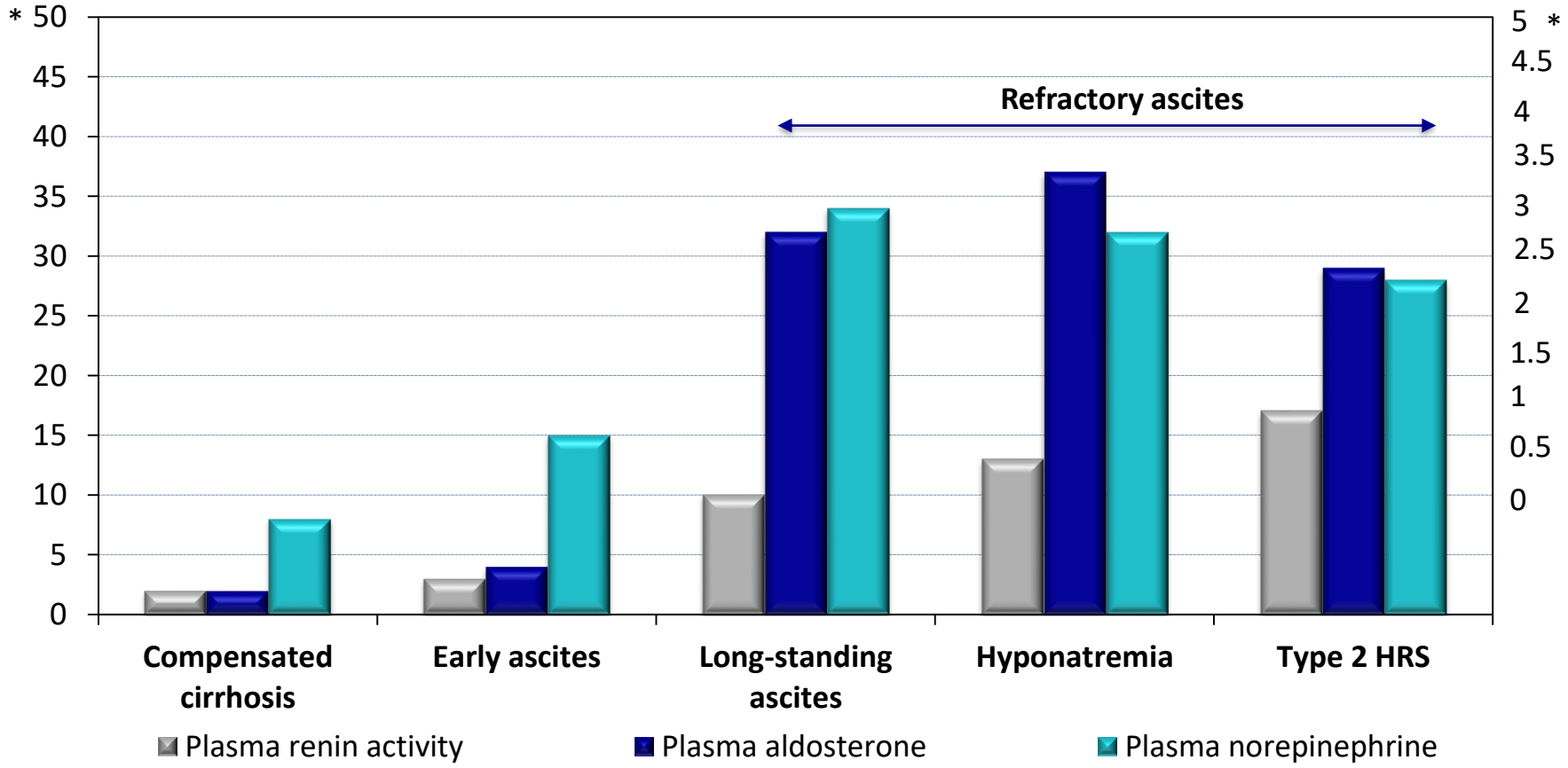
- Pathophysiology of decompensation and organ failures in patients with cirrhosis
- Evolution and classification of decompensation in patients with cirrhosis

Natural history of cirrhosis



Adapted from A. Albillos et al. Dis. Markers. 2011 ; 31 : 121-128

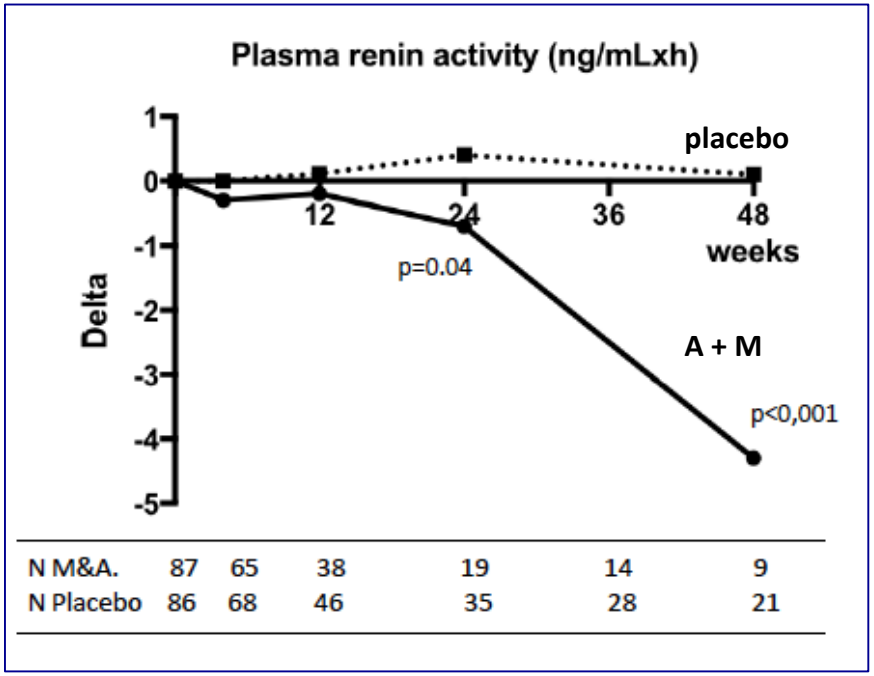
Increase in endogenous systemic vasoactive and sodium-retaining molecules in cirrhosis

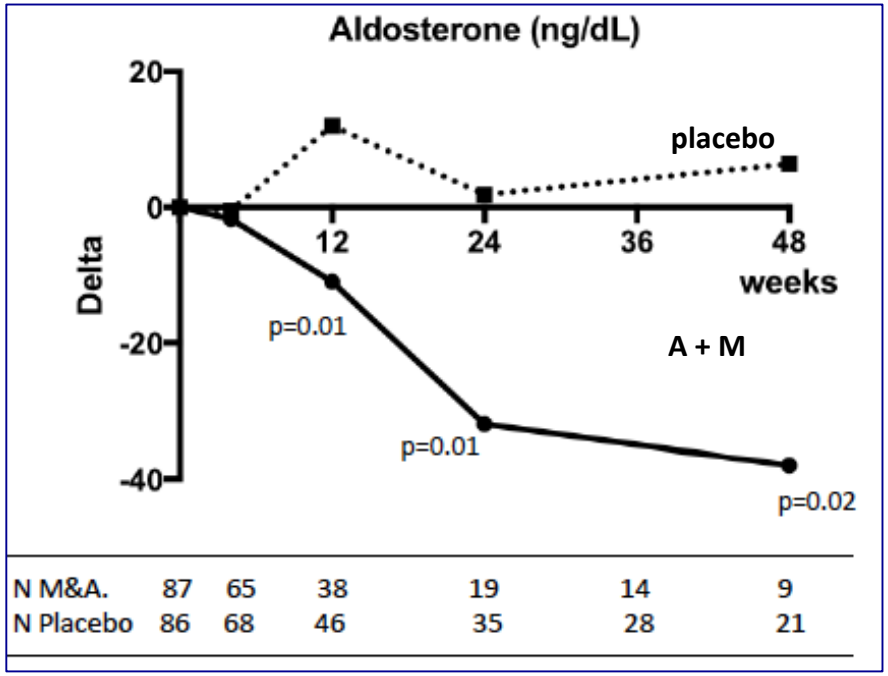


* = times versus compensated cirrhosis

M. Bernardi et al. J. Hepatol. 2015 ; 63 : 1272-1284

Effects of albumin (A) at a dose of 40g/15 days plus midodrine (M) at a a dose of 15-30 mg/day versus placebo in patients with cirrhosis and ascites

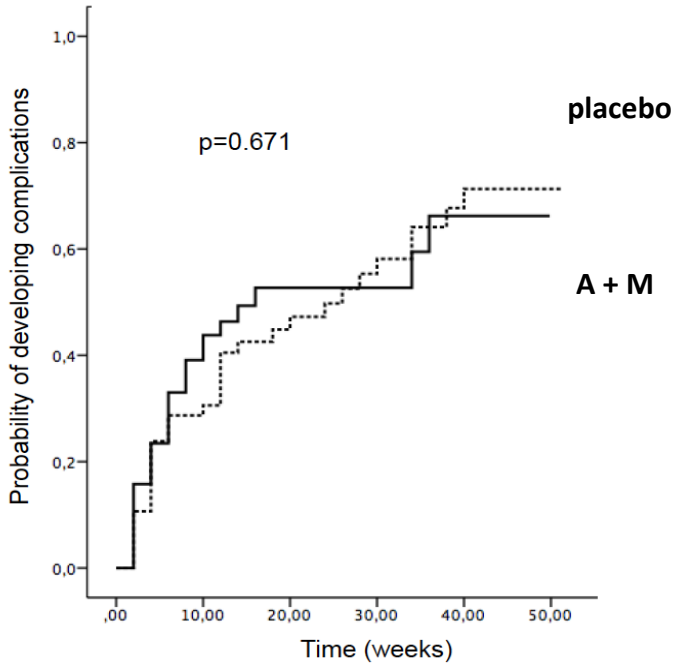




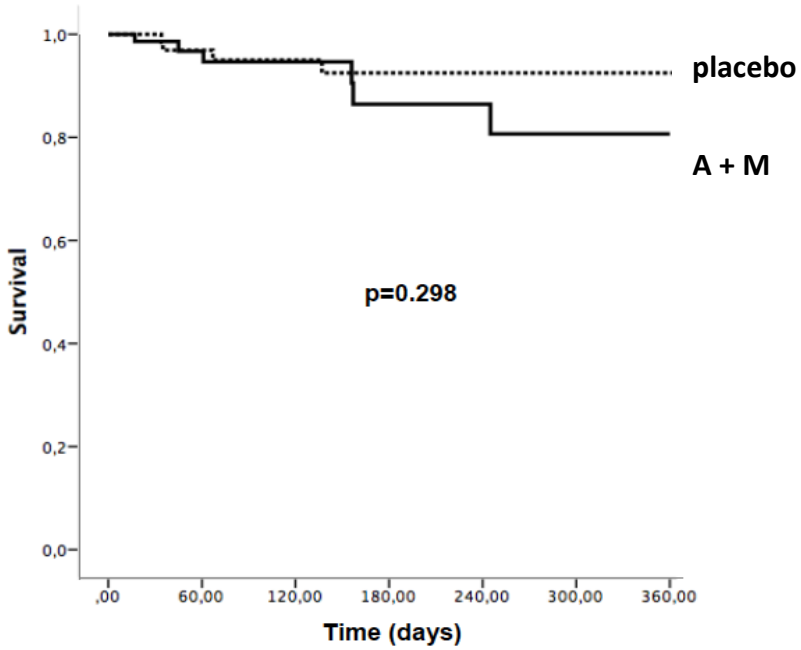
E. Sola et al. J Hepatol. 2018 ; 69 : 1250-1259

Effects of albumin (A) at a dose of 40g/15 days plus midodrine (M) at a a dose of 15-30 mg/day versus placebo in patients with cirrhosis and ascites

Probability of developing complications



One year survival



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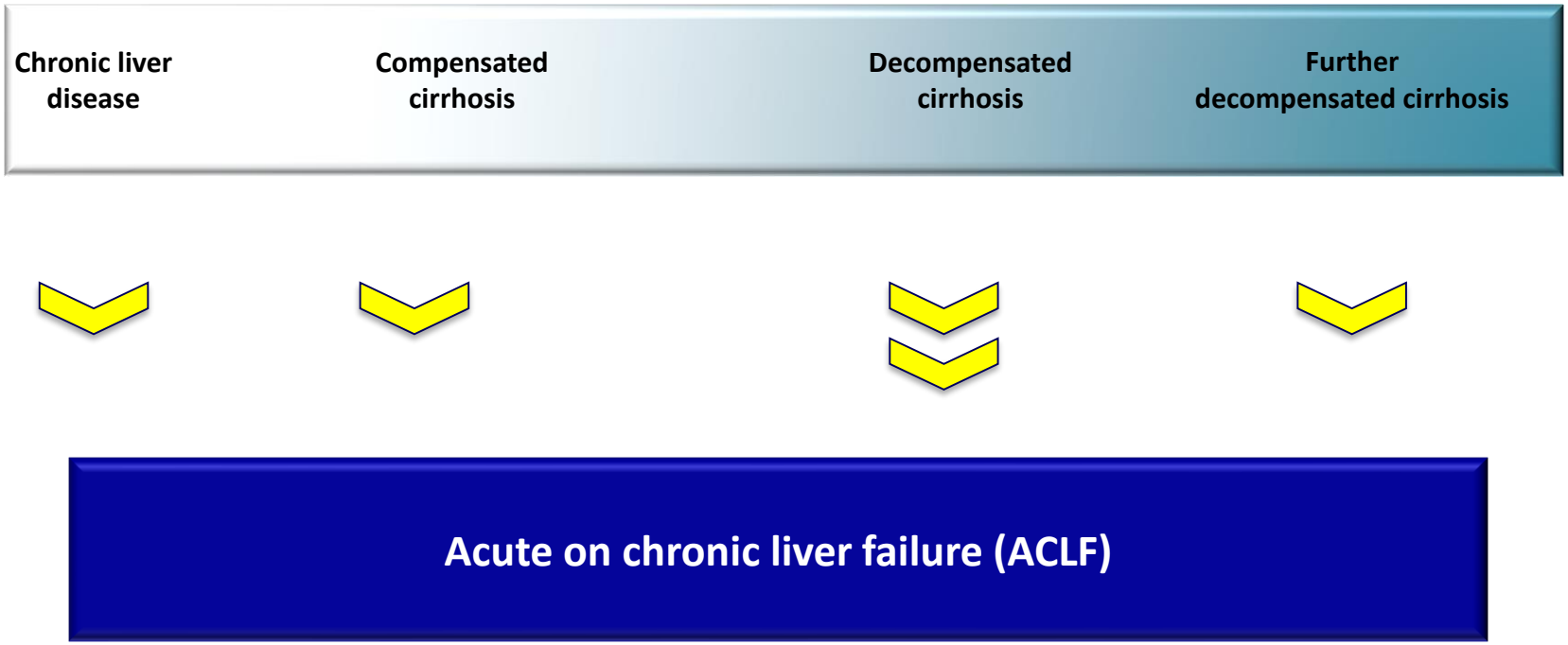
Natural history of cirrhosis



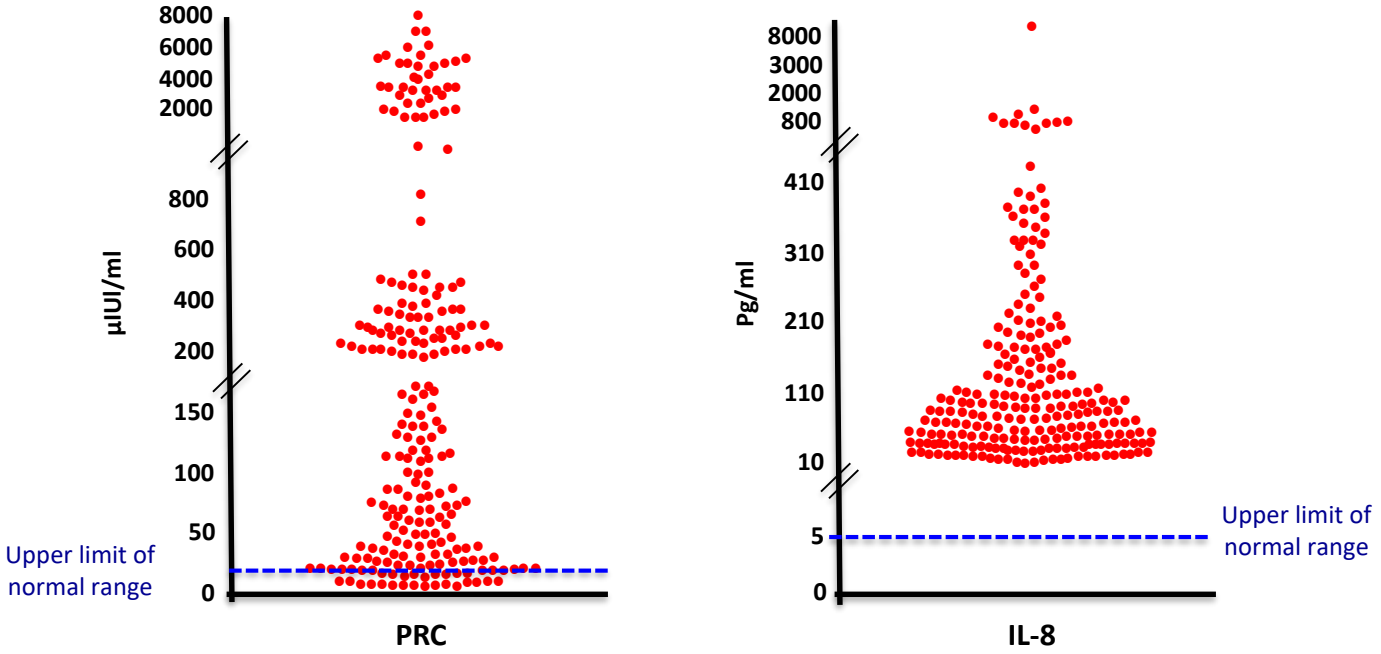
Adapted from R. Jalan et al. Gastroenterology 2014 ; 147 : 4-10

EASL CLIF diagnostic criteria

- Cirrhosis
- Acute decompensation
- Development of organ failure/s
- 28 day mortality rate > 15 %

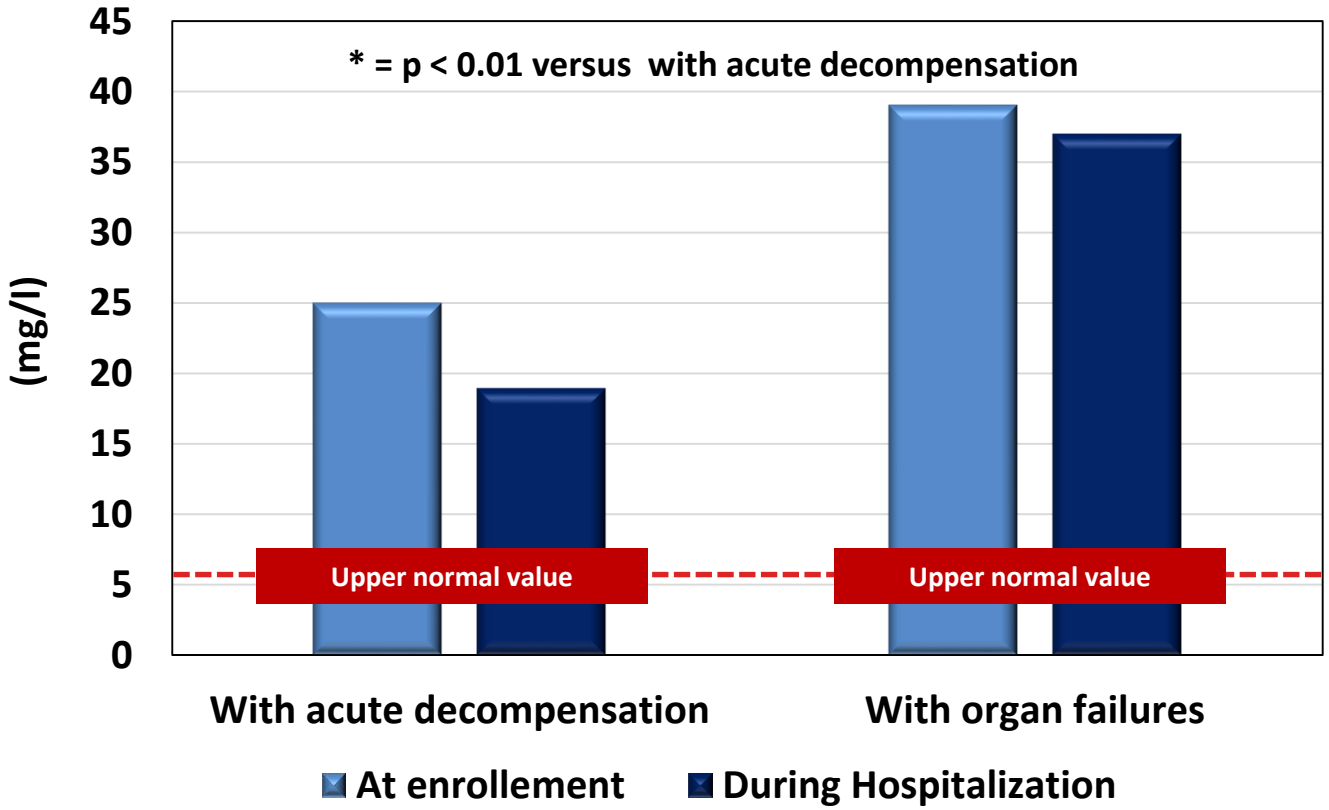
R. Moreau et al. (Canonic study) Gastroenterology 2013 ; 144 : 1426-1437

Individual values of plasma renin concentration (PRC) and IL-8 in patients with ACLF



J. Claria et al. Hepatology 2016 ; 64 : 1249-1264

C reactive protein values in patients with acute decompensation and in those with organ failures



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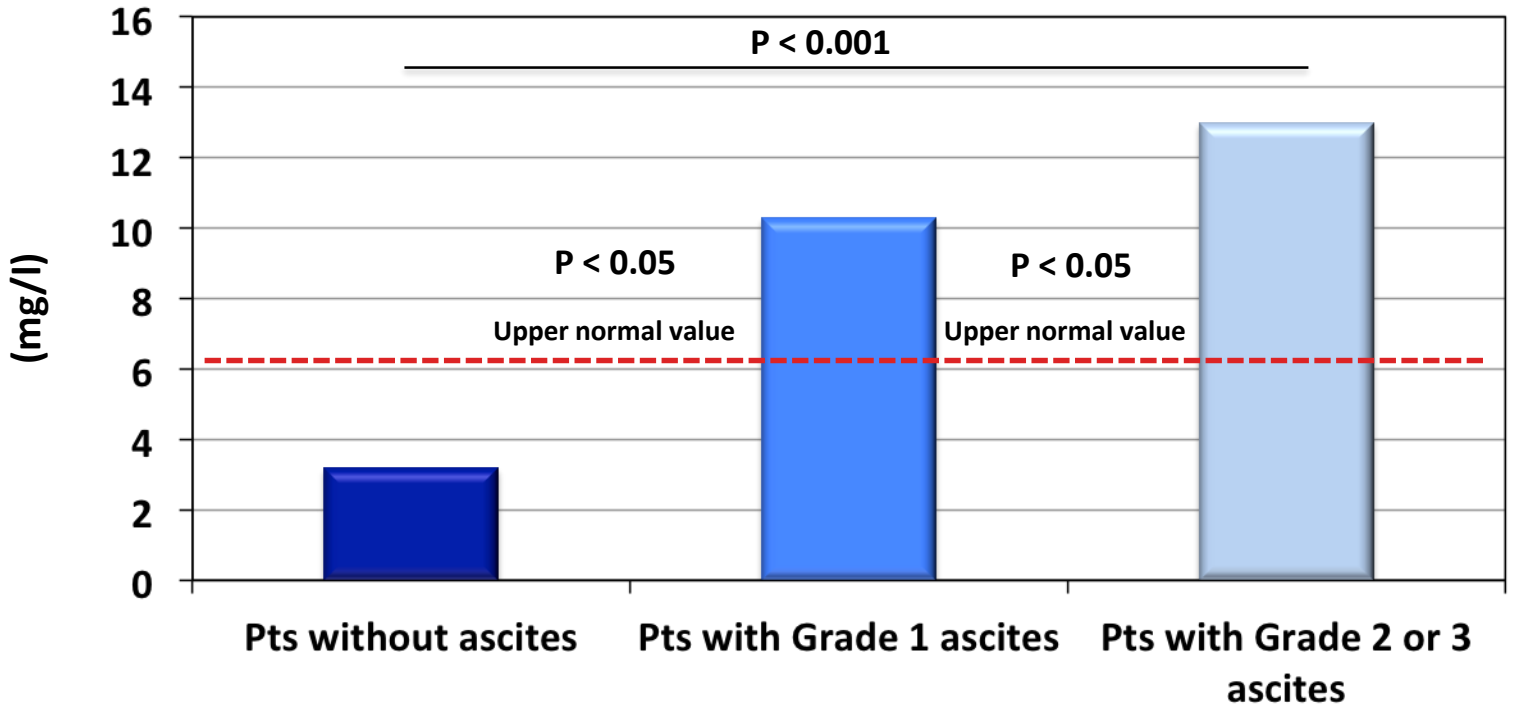
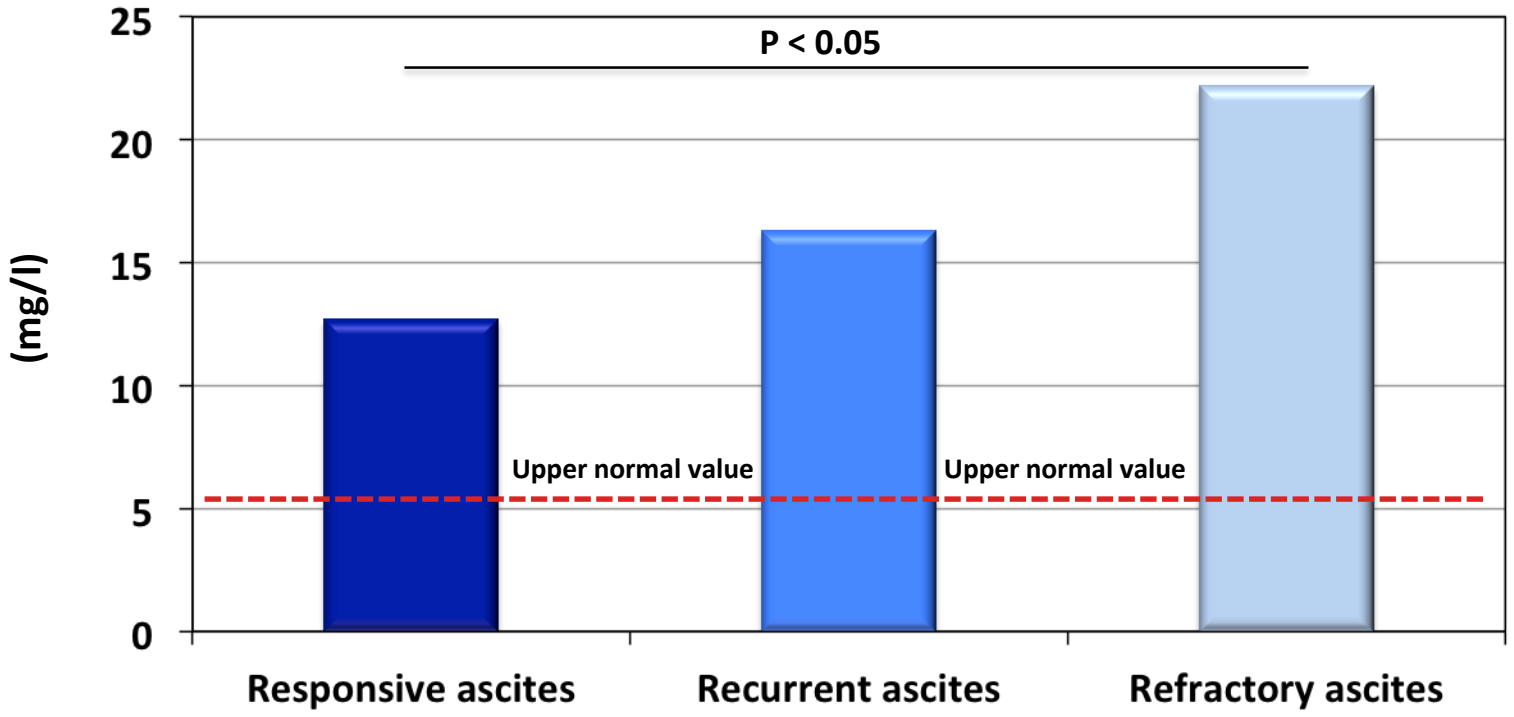
C-reactive protein in patients with cirrhosis according to the type of ascites



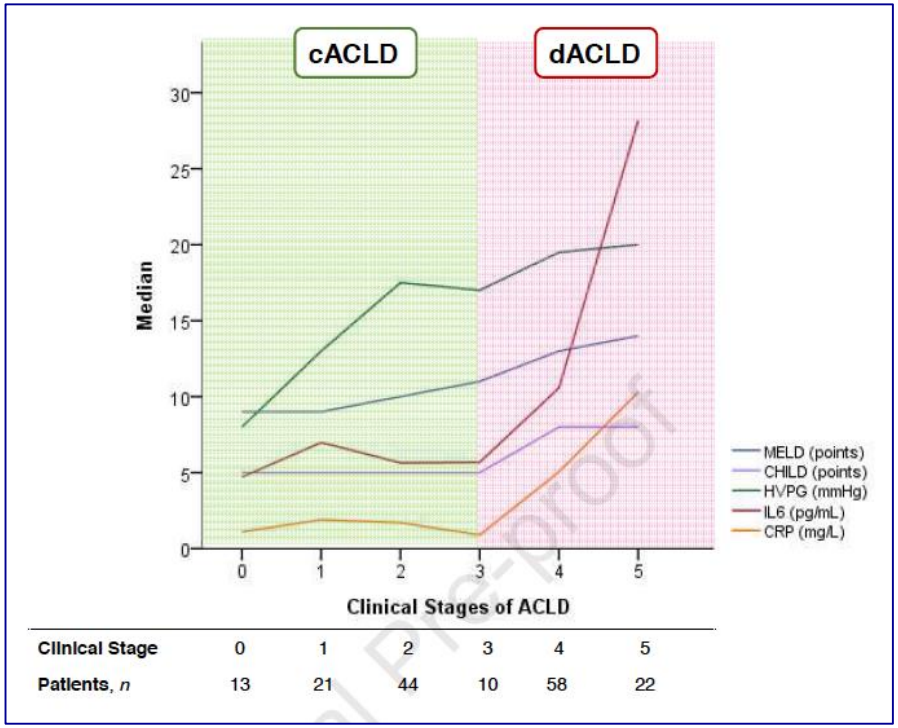
M. Tonon et al. Clin. Gastroenterol. Hepatol. 2021 ; 19 : 358-366

C-reactive protein in patients with cirrhosis according to the type of ascites



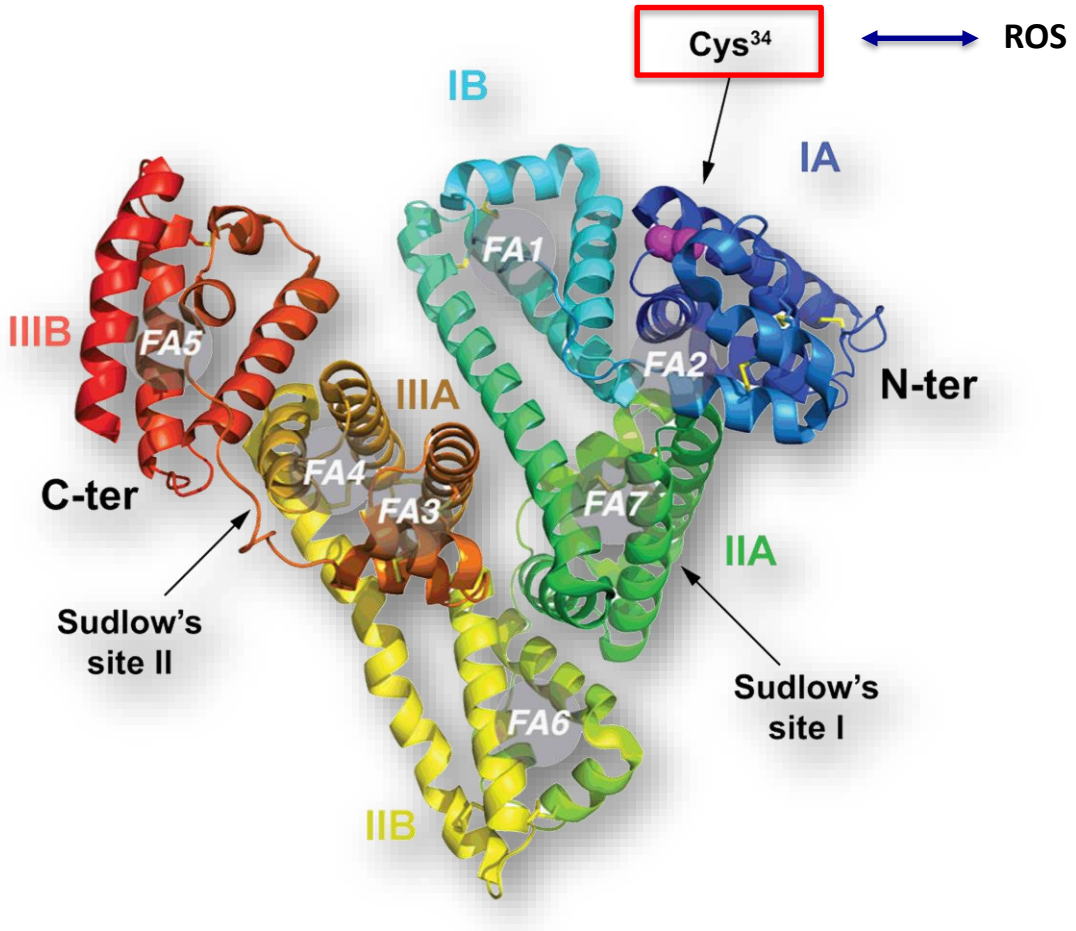
M. Tonon et al. Clin. Gastroenterol. Hepatol. 2020 ; 19 : 358-366

Dynamics of median MELD, CTP, HVPG, CRP, and IL-6 serum levels across compensated (c) and decompensated (d) stages of chronic liver diseases (ACLD)



D. Costa et al. J. Hepatol. 2021 ; 74 : 819-828

Albumin molecule with the main binding domains



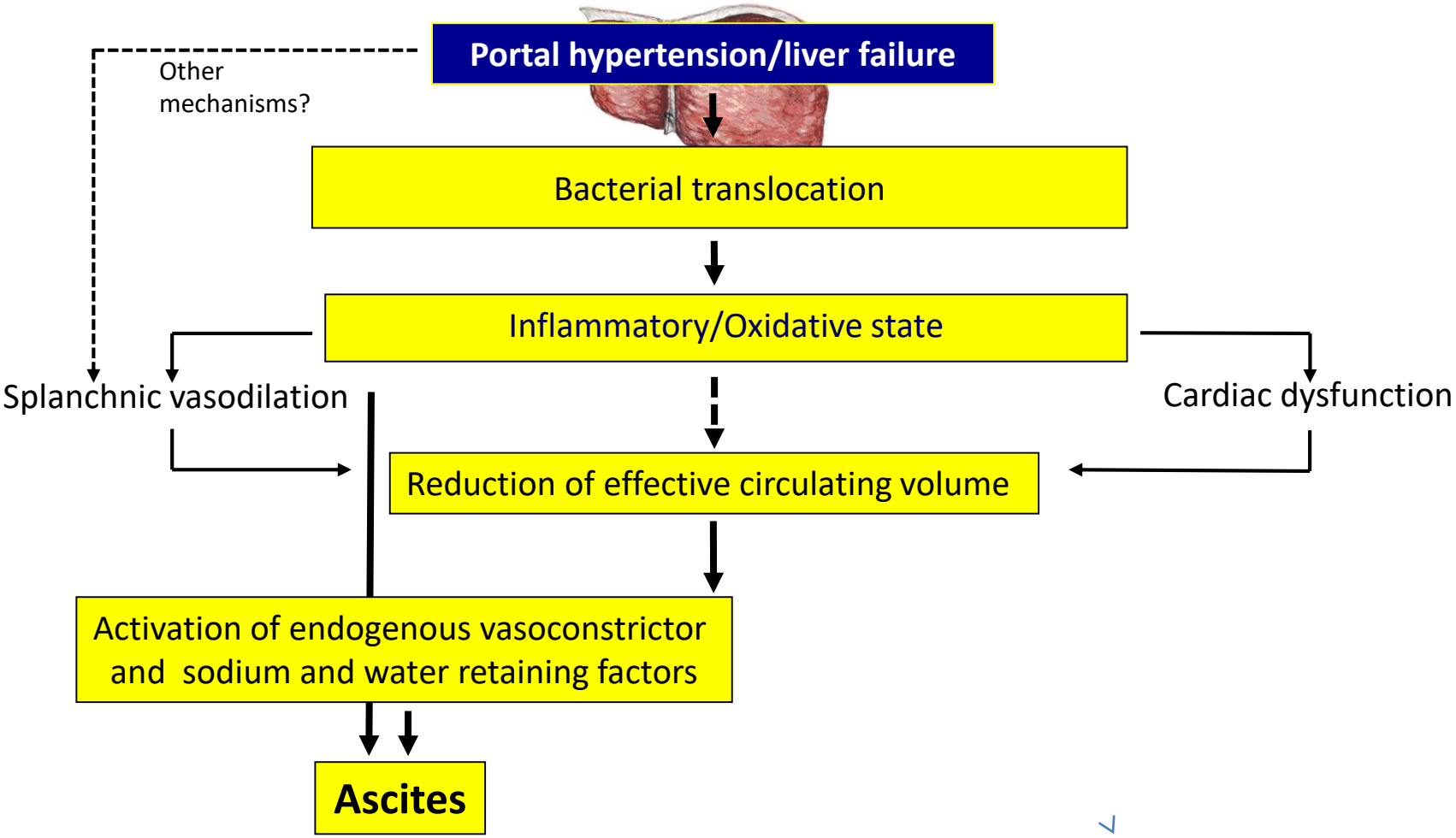
R. Jalan et al. Hepatology 2013 ; 59 : 918-920

Albumin oxidation fractions in patients with cirrhosis

	Healthy Subjects (n° = 40)	AD (n°= 285)	ACLF (n° = 237)	P
HMA (%)	71 (68-74)	53 (42.62)	45 (33-56)	< 0.001
HNA_1+ HNA_2 (%)	28 (25-30)	46.4 (37.5-56.9)	51.8 (42.2-65.6)	<0.001
HNA_2 (%)	1.3 (0.3-0.9)	4.5 (2.5-8.8)	9.8 (5.6-14.8)	< 0.001

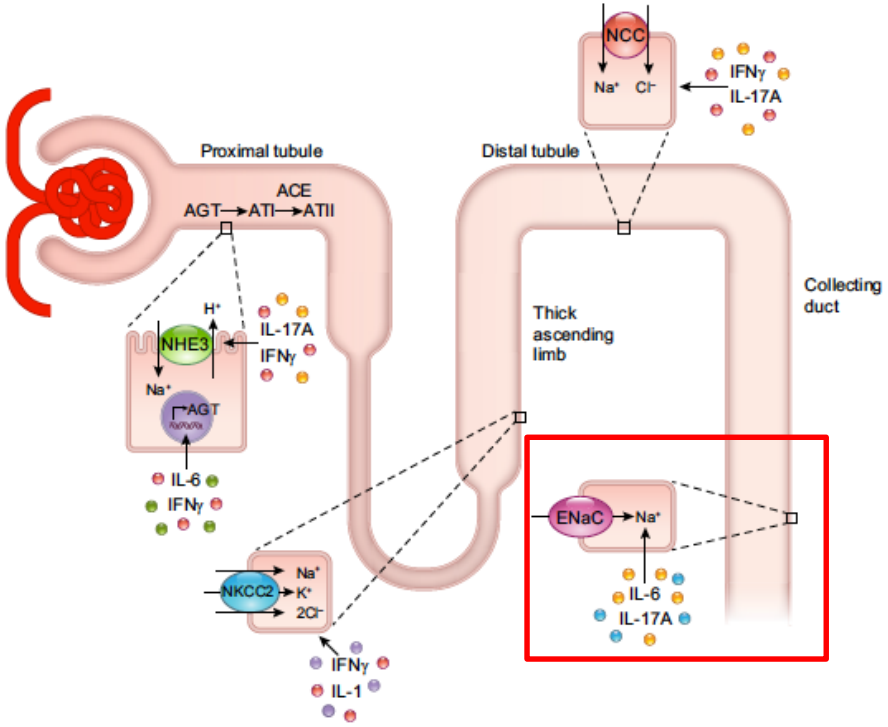
J. Claria et al. Hepatology 2016 ; 64 : 1249-1264

New pathophysiological hypothesis



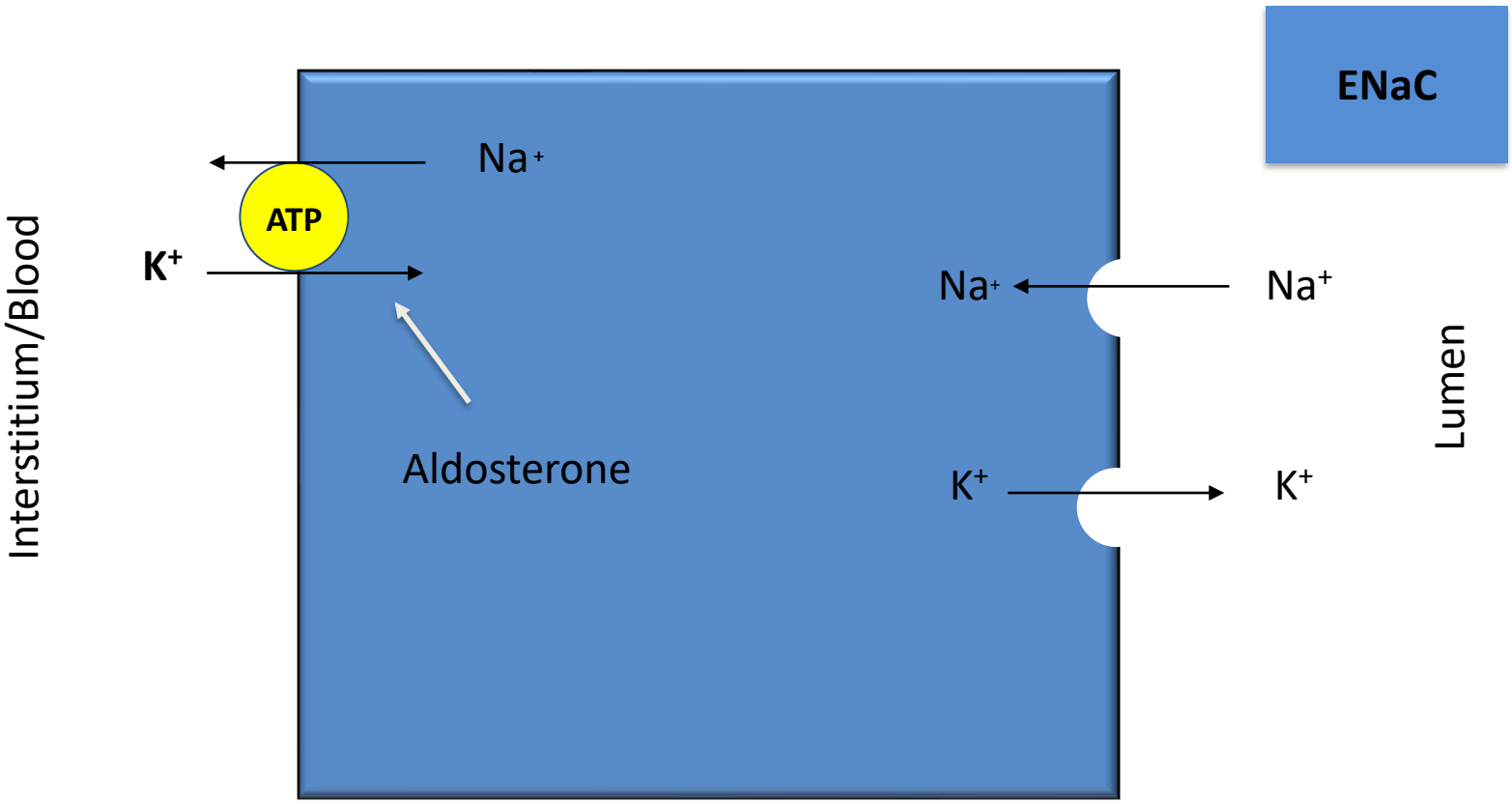
Adapted from M. Bernardi et al. J. Hepatol. 2015 ; 63 : 1272 - 1284

Reanal trasporters activated by inflammatory cytokines

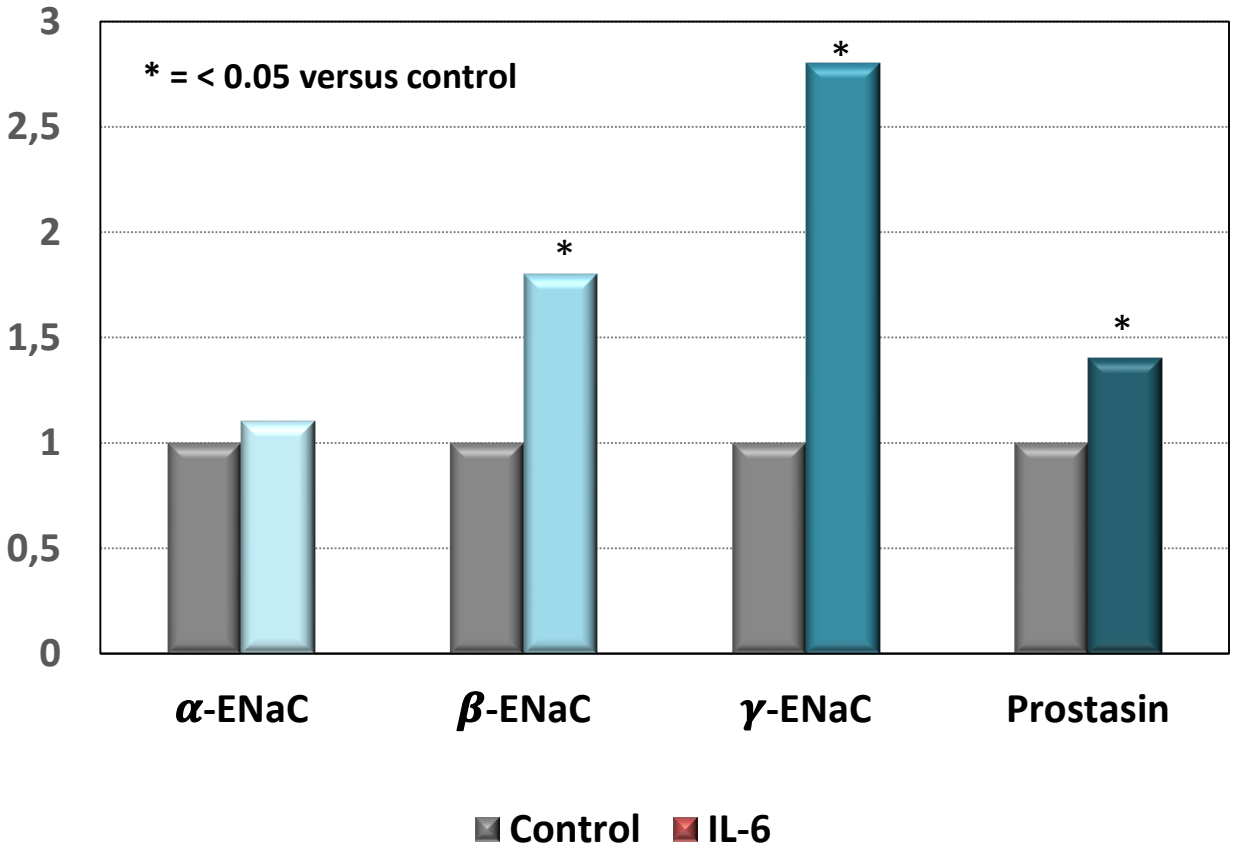


A.E. Norlander et al. Am. J. Renal Physiol. 2017 ; 313 : F141-F144

Mechanisms of sodium reabsorption in the collecting duct



Effects of IL-6 on the gene expression of ENaC subunits and prostasin



K. Li et al. Am J Physiol Regul Integr Comp Physiol. 2010 ; 299 : R590-R595

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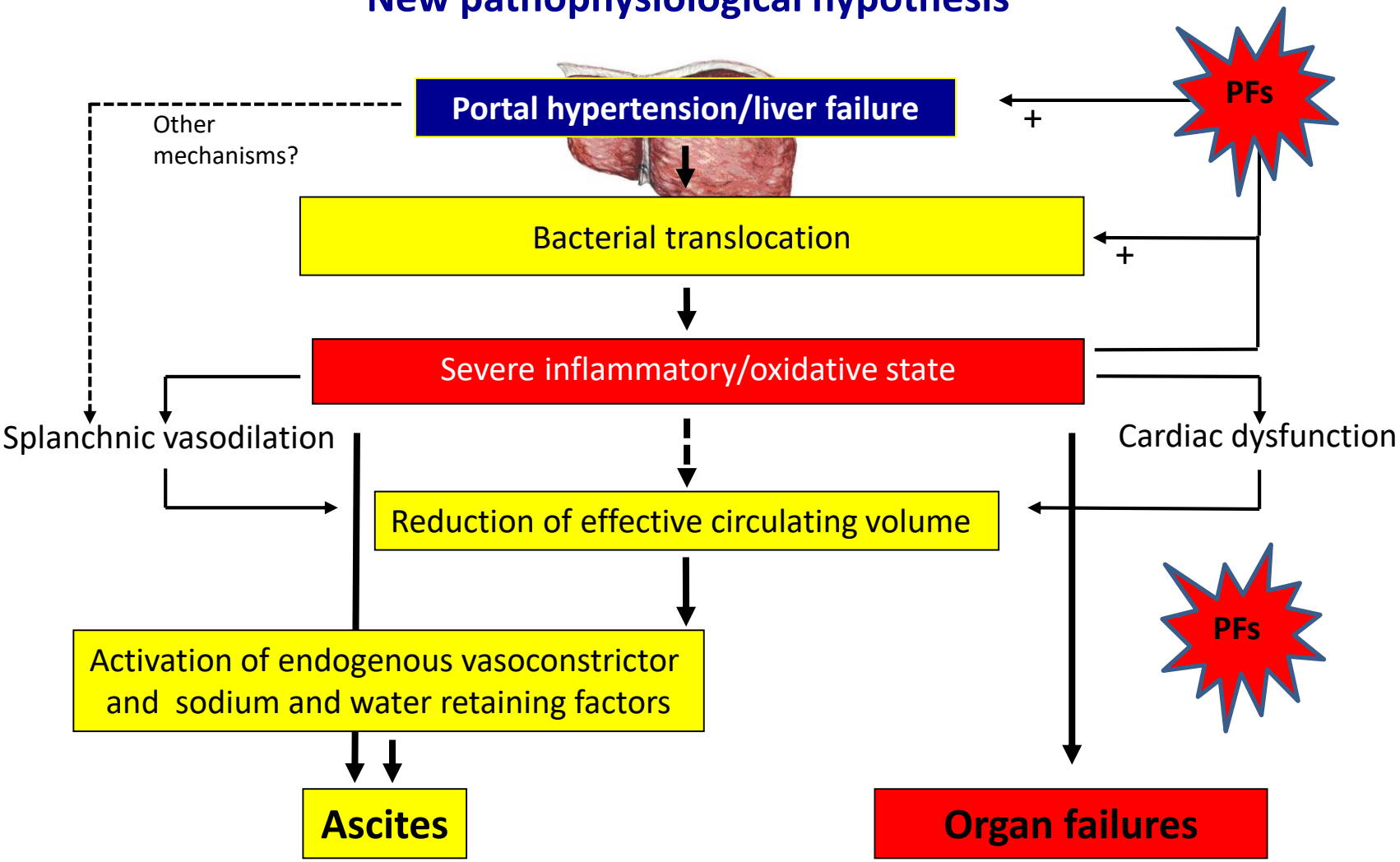

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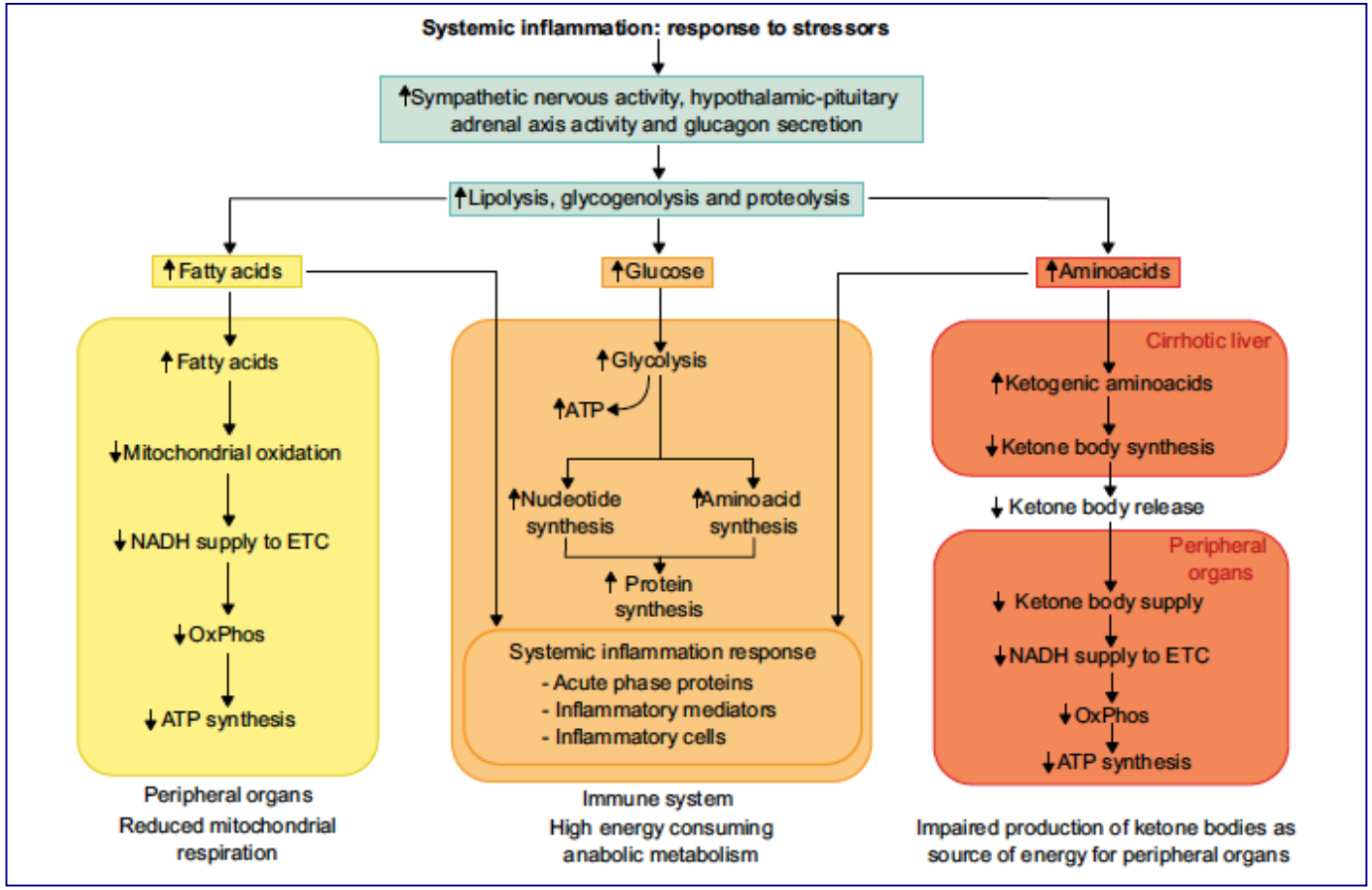
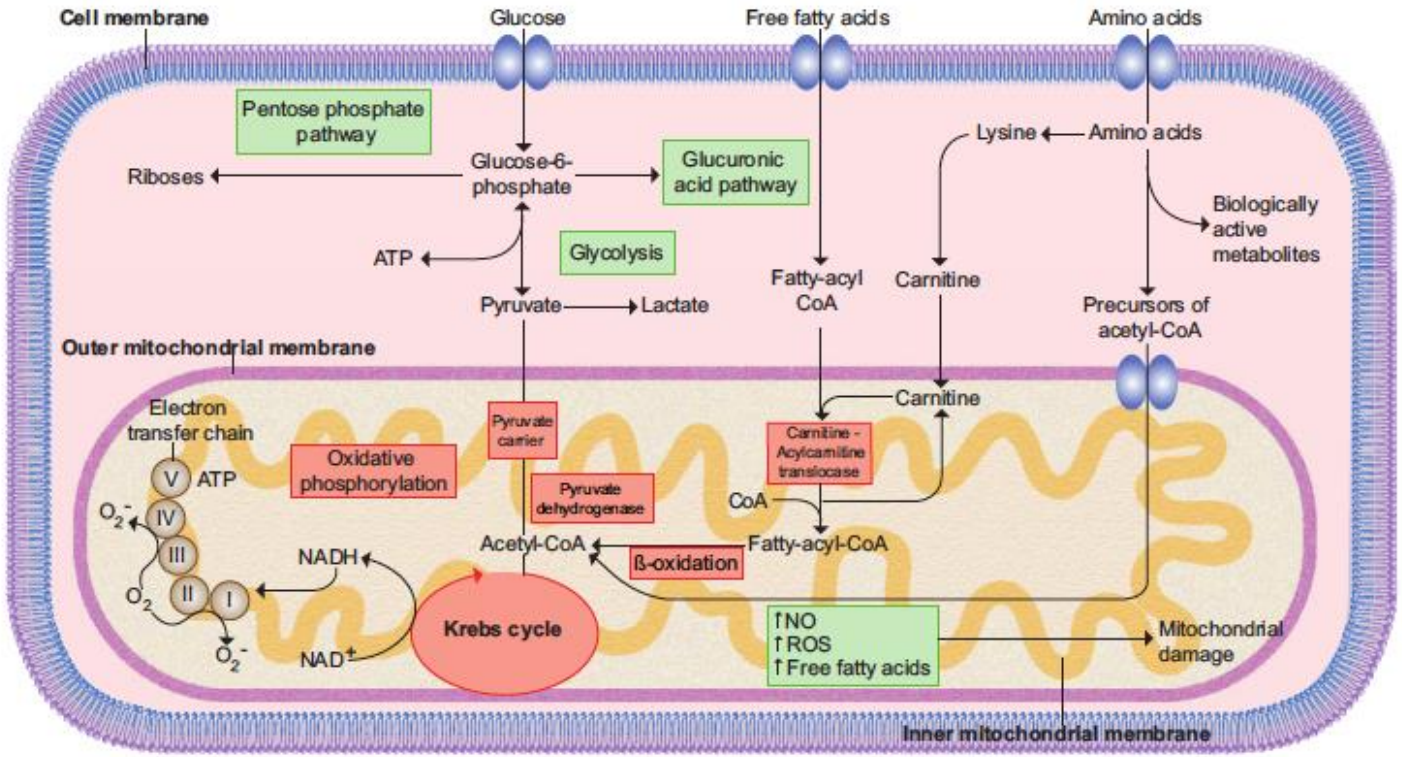
Impaired function and damage of mitochondria in patients with AD



V. Arroyo et al. J. Hepatol. 2021 ; 74 : 670-685

Impaired function of mitochondria and mitochondria damage in patients with AD



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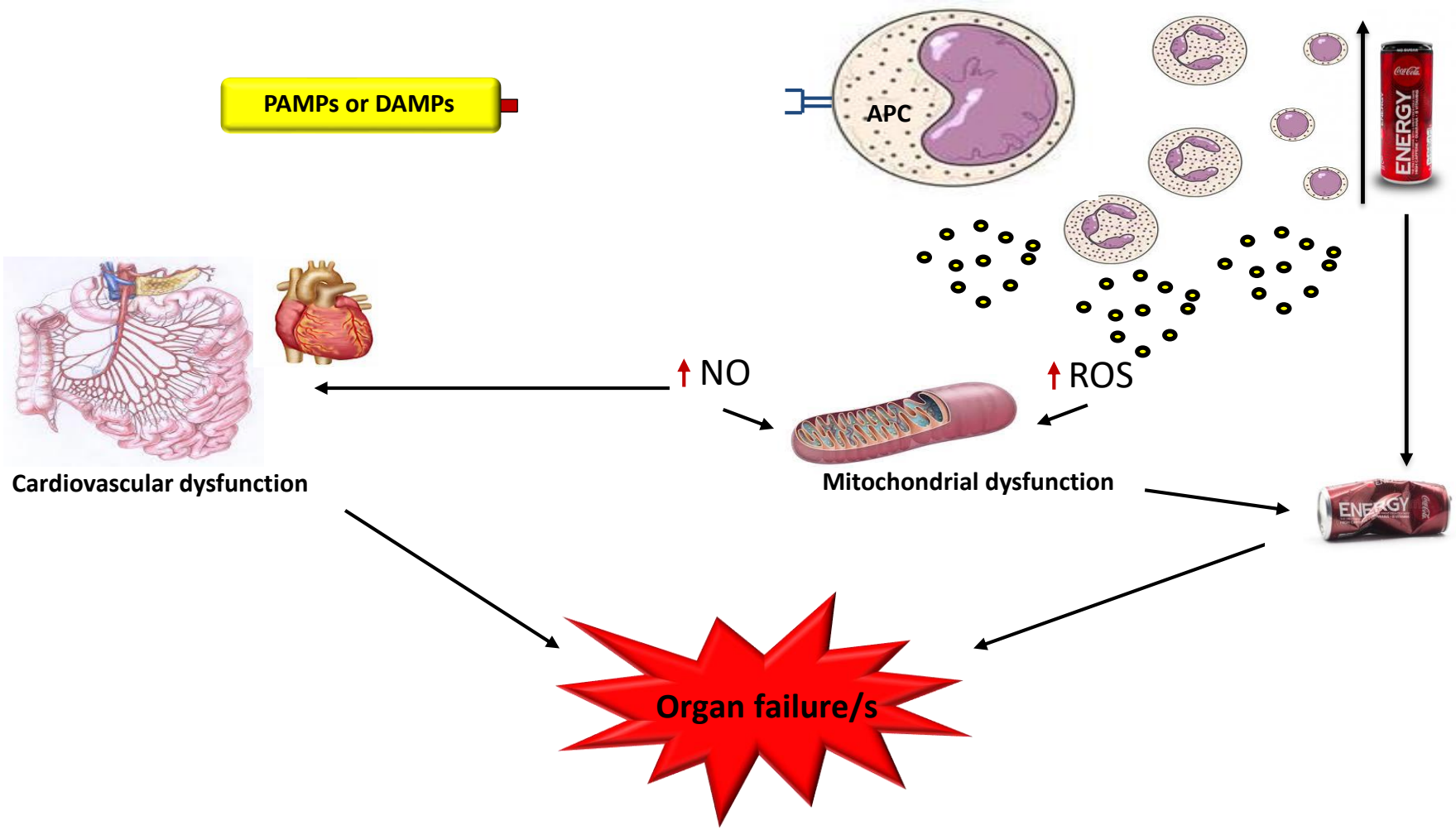
Pathogenesis of organ failure/s



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- Cirrhosis
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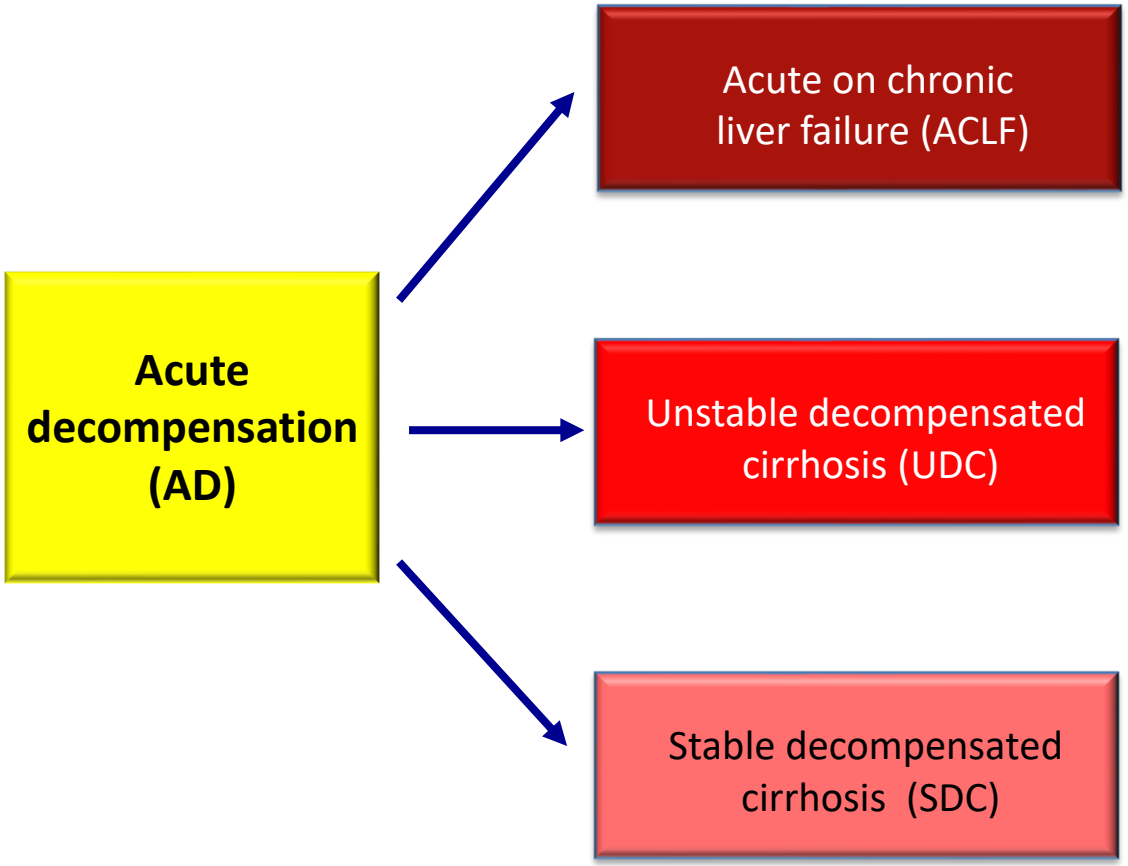
R. Moreau et al. (Canonic study) Gastroenterology 2013 ; 144 : 1426-1437

Dynamics and classification of decompensation in patients with cirrhosis

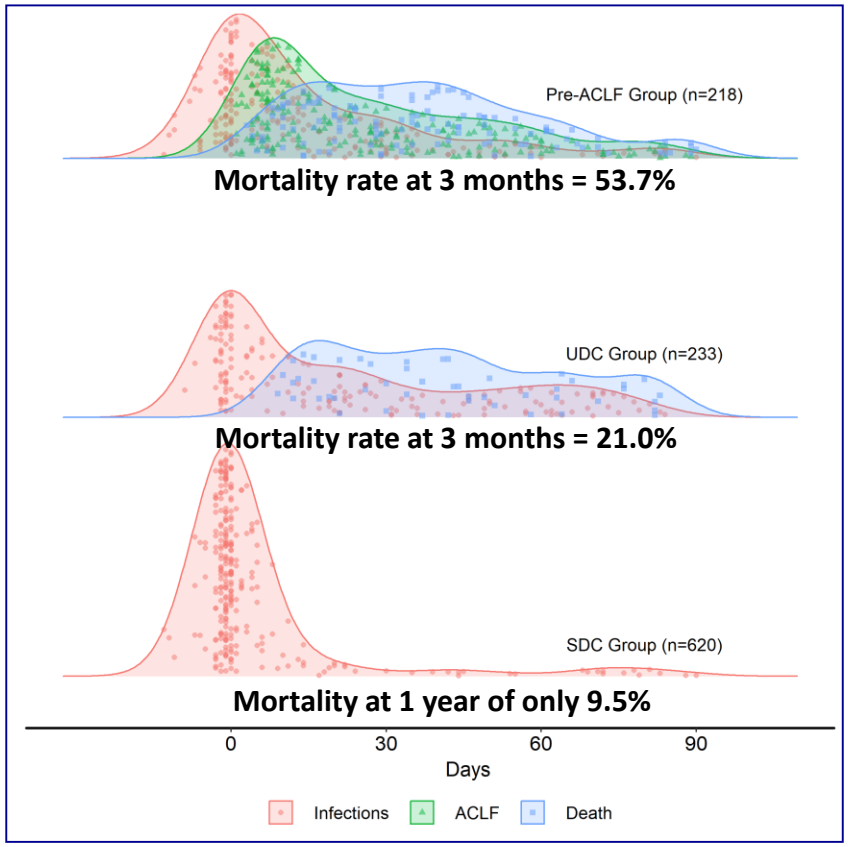


Trajectories in patients with cirrhosis admitted to the hospital for AD

218/1071

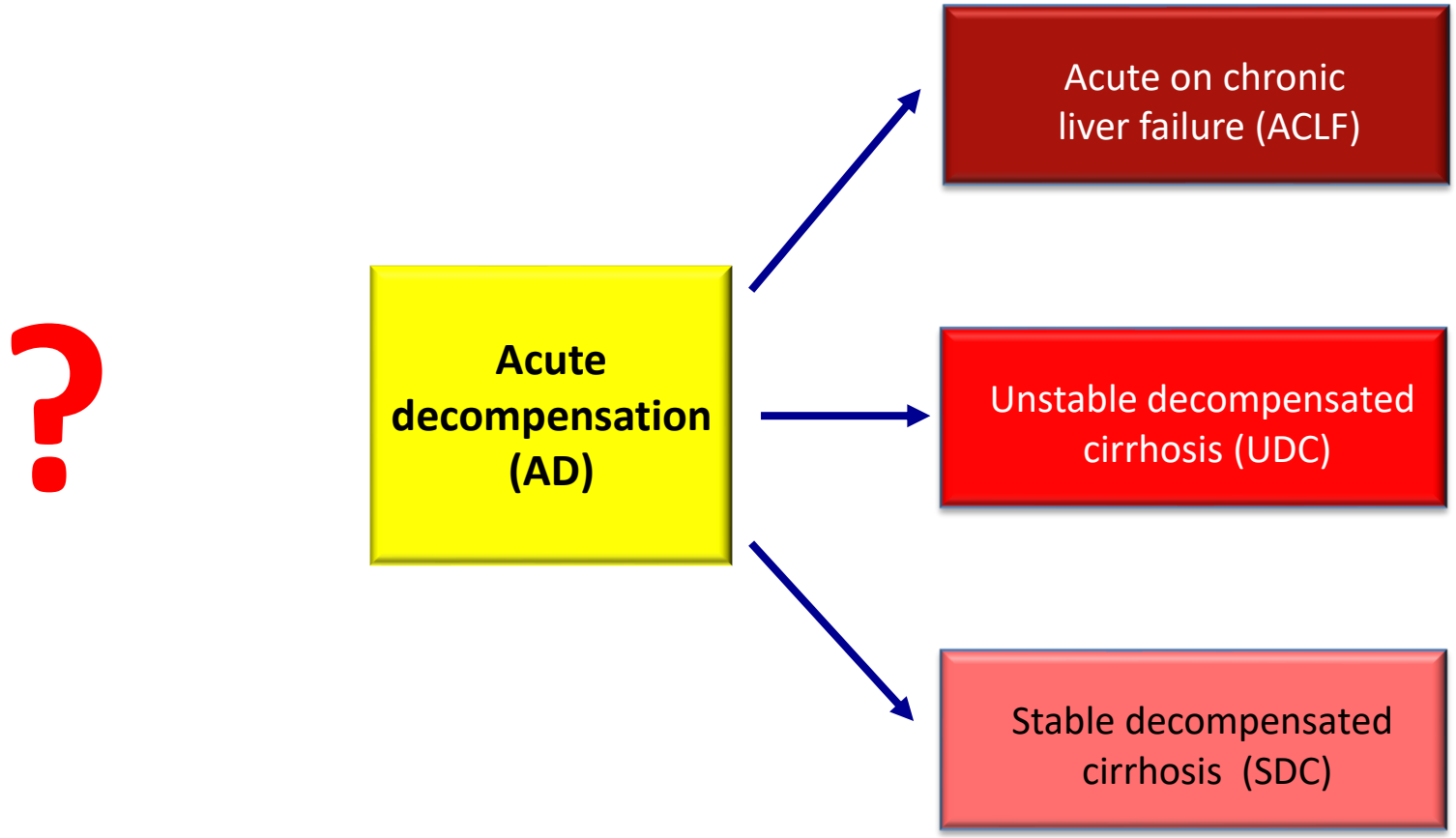
233/1071

620/1071

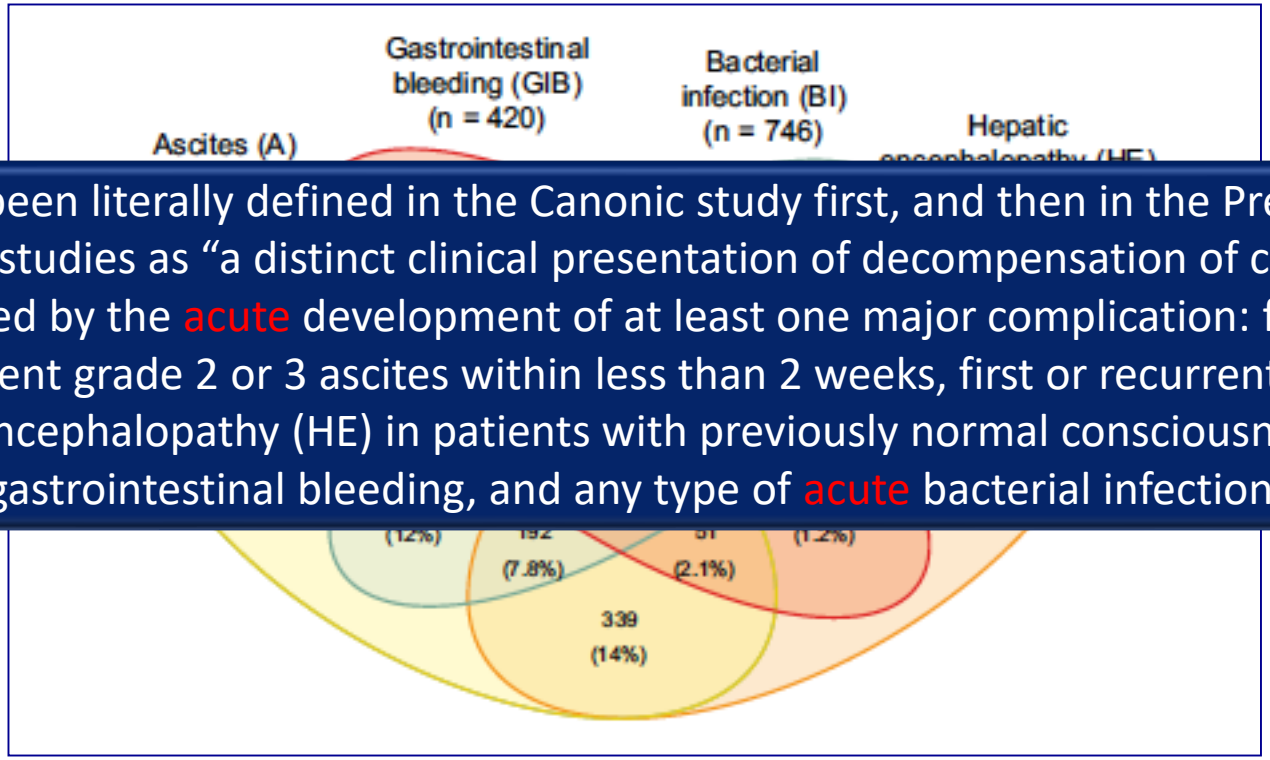


J. Trebicka et al. (Predict study 1) J. Hepatol. 2020 ; 73 : 842-854

Dynamics and classification of decompensation in patients with cirrhosis



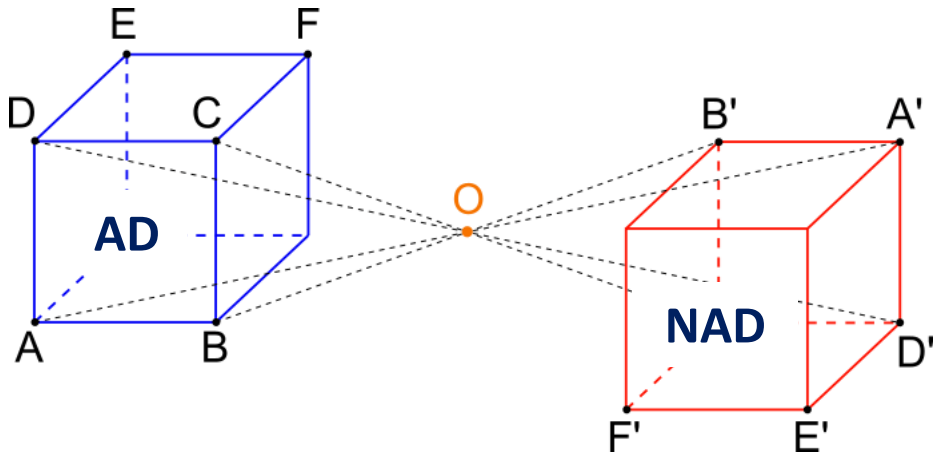
Definition of acute decompensation



AD has been literally defined in the Canonic study first, and then in the Predict and Aclara studies as “a distinct clinical presentation of decompensation of cirrhosis defined by the acute development of at least one major complication: first or recurrent grade 2 or 3 ascites within less than 2 weeks, first or recurrent acute hepatic encephalopathy (HE) in patients with previously normal consciousness, acute gastrointestinal bleeding, and any type of acute bacterial infection”

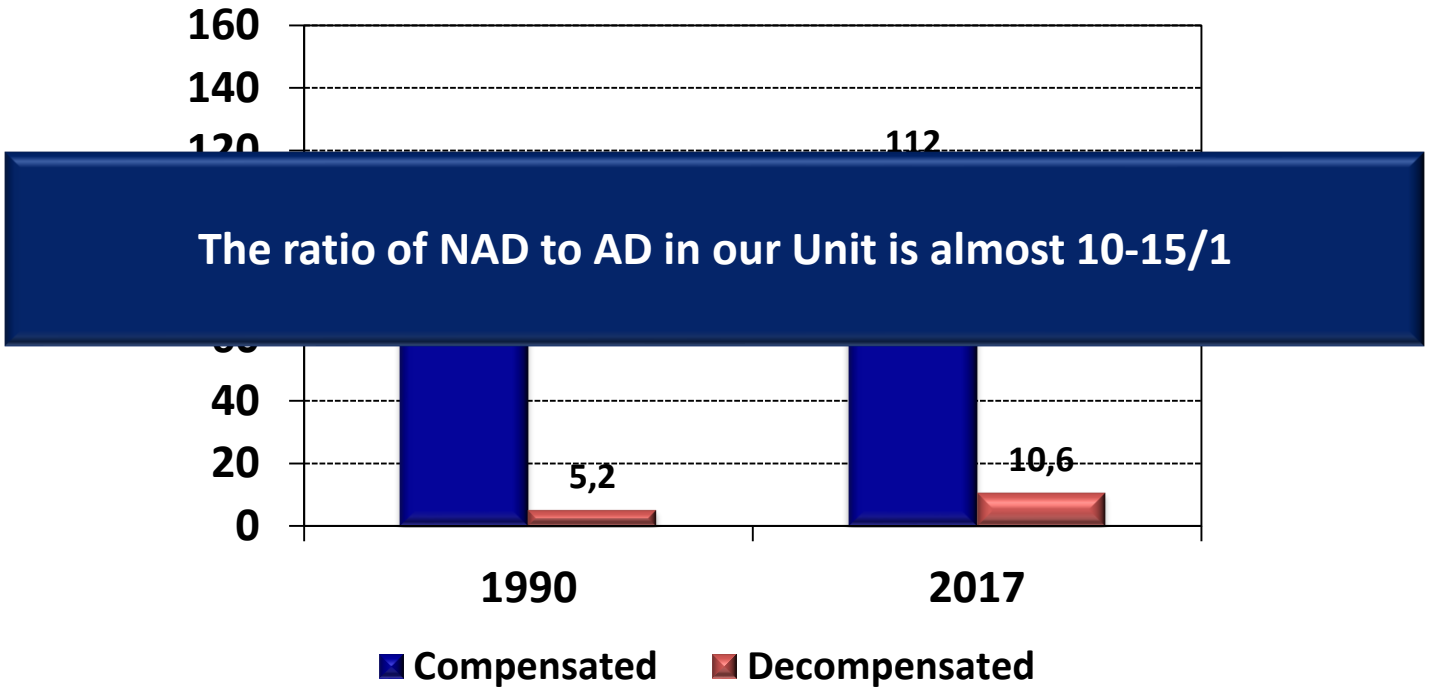
V. Arroyo et al. J. Hepatol. 2021 ; 74 : 670-685

Visual concept of symmetry



Even just for a simple concept of symmetry
if one defines one fact as acute she/he implicitly defines another as not acute

Number of prevalent cases of compensated and decompensated cirrhosis in 1990 and 2017



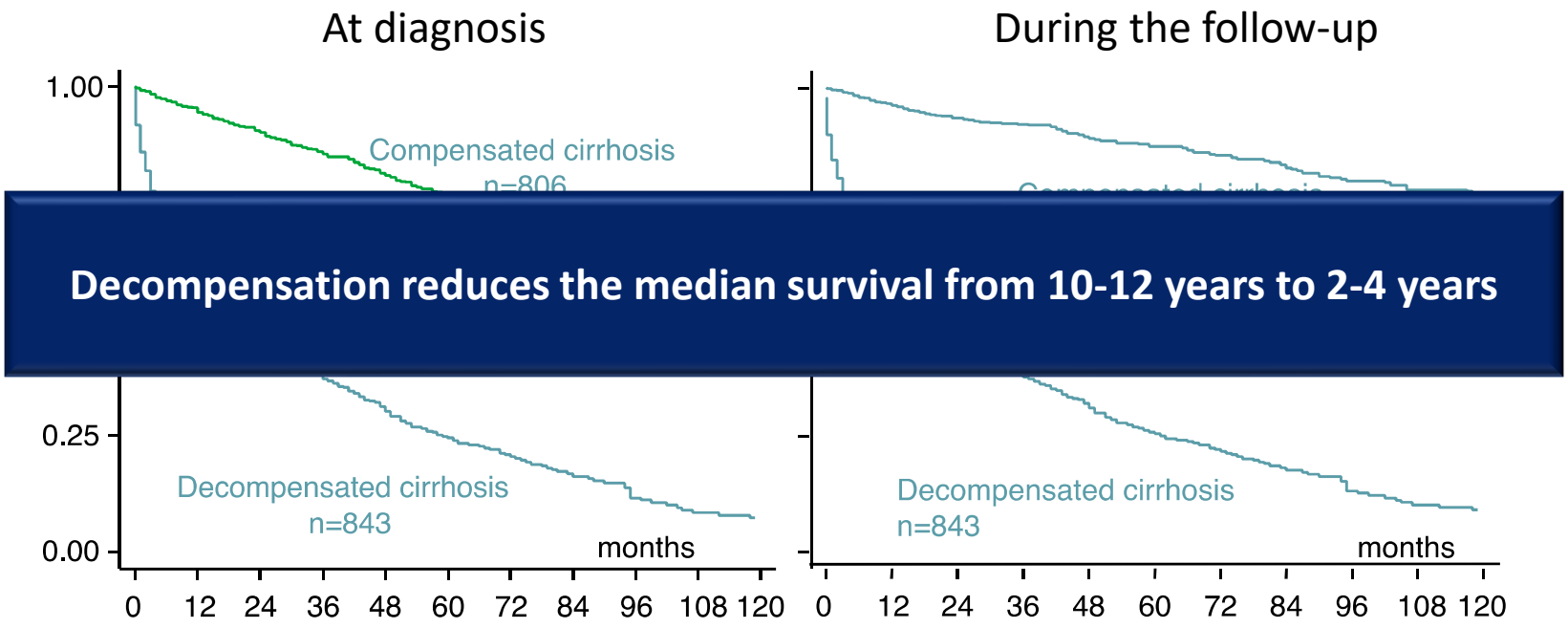
The ratio of NAD to AD in our Unit is almost 10-15/1

Lancet 2020 ; 5 : 245-266

Dynamics and classification of decompensation in patients with cirrhosis

- Other definitions have been introduced on the natural history of cirrhosis such as: first decompensating event and further decompensation.

Survival according to the main stage of cirrhosis



Decompensation reduces the median survival from 10-12 years to 2-4 years

G. D'Amico et al. J. Hepatol. 2006 ; 44 : 217-231

Five year outcomes in patients with cirrhosis

Stage	Definition	Five year mortality rate (%)
1	Compensated cirrhosis without varices	1.5%
2	Compensated cirrhosis with varices	10%
3	Bleeding without other complications	20%
4	First non bleeding decompensating event	30%

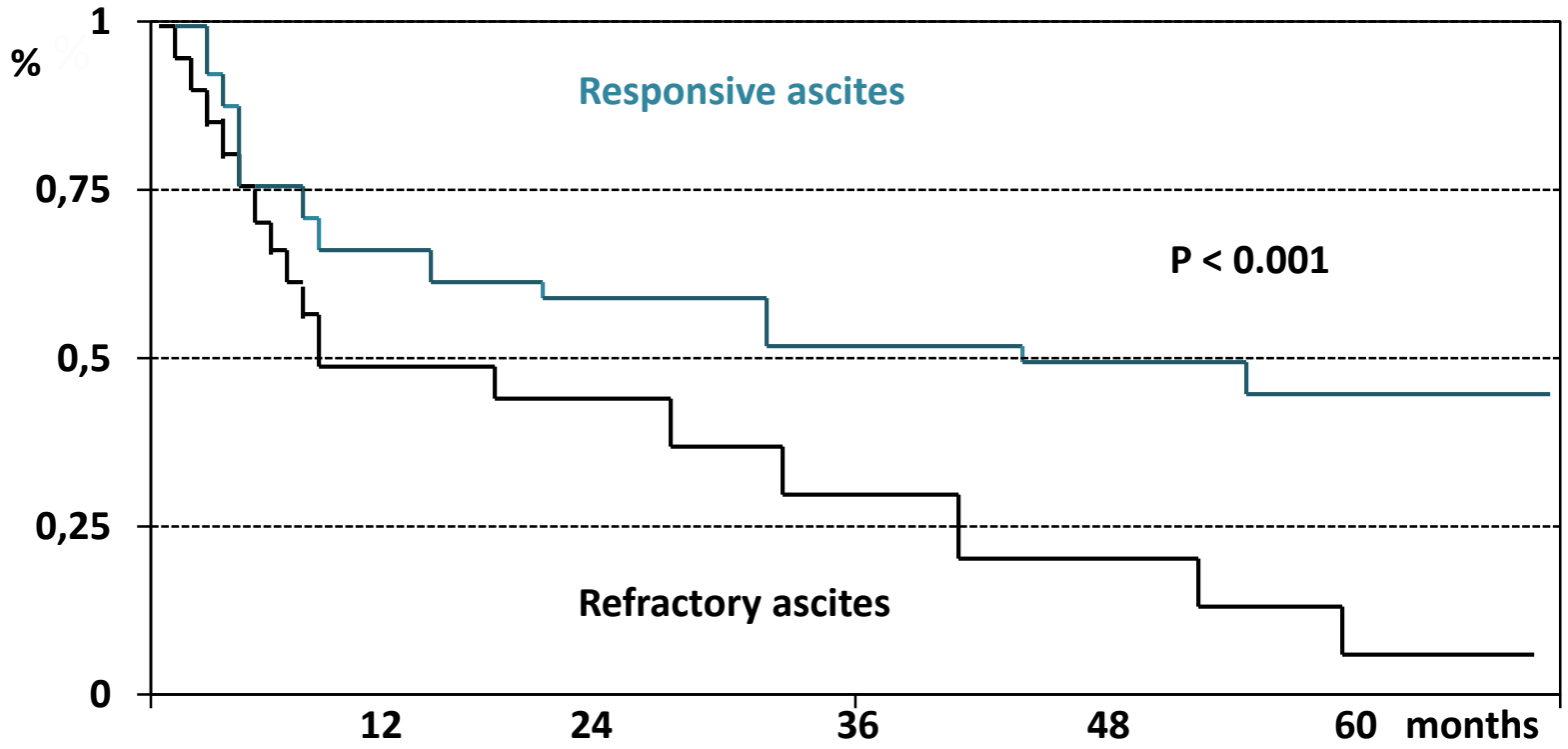
G. D'Amico et al. Alment. Pharmacol. Ther 2014 ; 39 : 1180-1193

Definition of further decompensation

Specific events that define further decompensation are any of the following:

- Development of a second portal hypertension-driven decompensating event (ascites, variceal haemorrhage or hepatic encephalopathy) and/or jaundice;
- Development of recurrent variceal bleeding, recurrent ascites (requirement of 3 or more large-volume paracenteses within 1 year), recurrent encephalopathy,
- Development of SBP and/or HRS-AKI;
- In patients presenting with bleeding alone, development of ascites, encephalopathy, or jaundice after recovery from bleeding but not if these events occur around the time of bleeding.

Probability of survival in cirrhotic patients with ascites



F. Salerno et al. Am. J. Gastroenterol. 1993 ; 88 : 514-519

Five year outcomes in patients with cirrhosis

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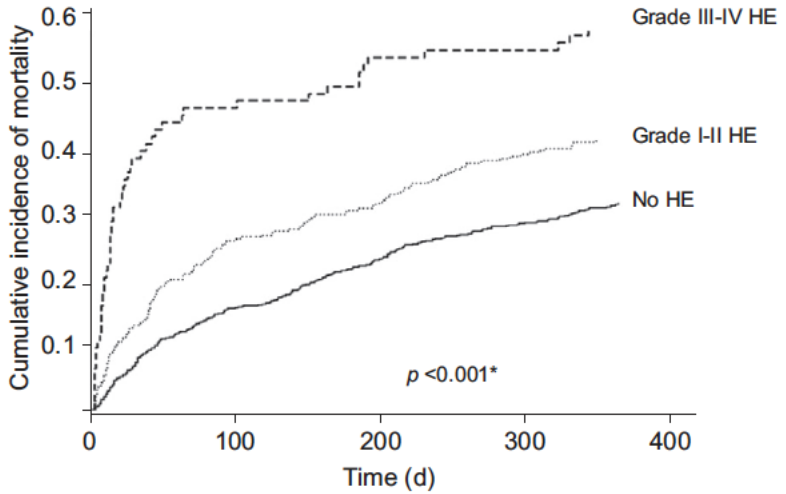
2	Compensated cirrhosis with varices	10%
3	Bleeding without other complications	20%
4	First non bleeding decompensating event	30%
5	Further decompensation	88 %

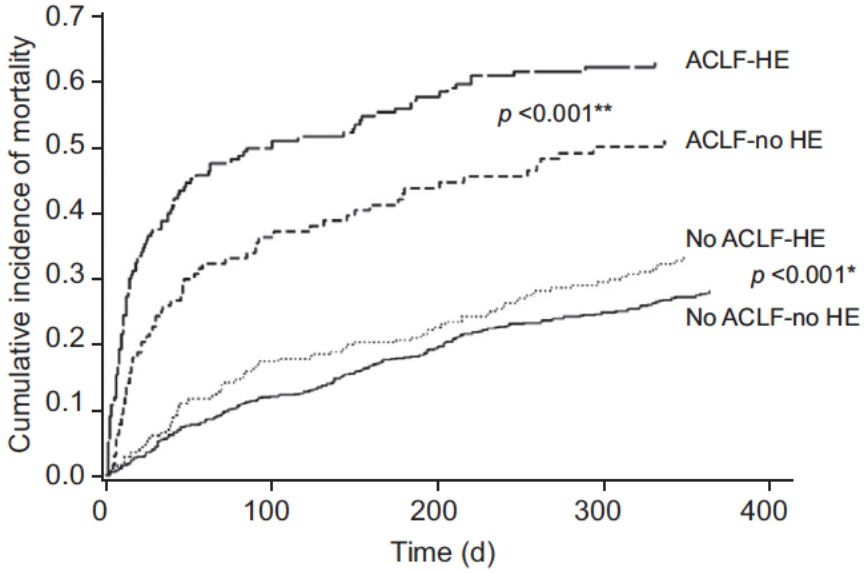
G. D'Amico et al. Alment. Pharmacol. Ther 2014 ; 39 : 1180-1193

Mortality of patients related to the severity of hepatic encephalopathy



J. Cordoba et al. J. Hepatol. 2014; 6 : 275-281

Mortality of patients with hepatic encepalophaty (HE) according to the diagnosis of acute on chronic liver failure (ACLF)



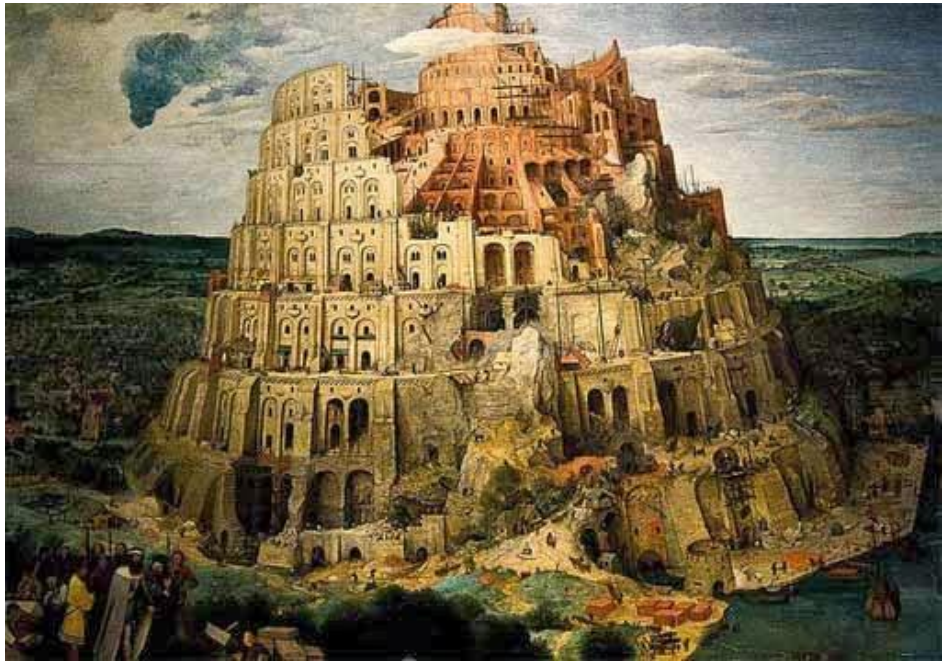
J. Cordoba et al. J. Hepatol. 2014; 6 : 275-281

Dynamics and classification of decompensation in patients with cirrhosis

- Other definitions have been introduced on the natural history of cirrhosis such as: first decompensating event and further decompensation.

- We think it's time to reflect and deepen these issues, laying the basis, if possible, to develop a global consensus in order to maintain research and literature coherence.

The Tower of Babel



Pieter Bruegel il vecchio, Grande torre di Babele, 1563, Kunsthistorisches Museum Vienna

New definition of decompensation in patients with cirrhosis

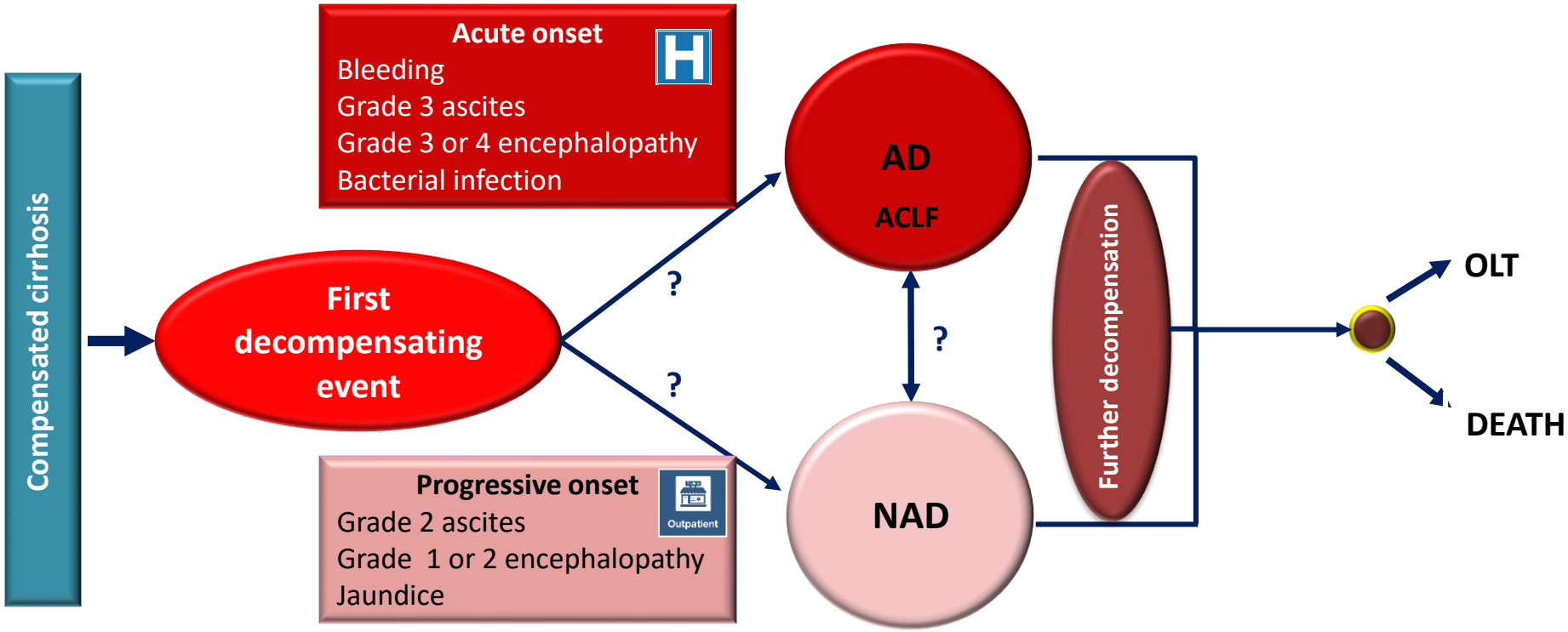
Venice, Lido (Italy) August 16th, 2023

Does it exist a non acute decompensation (NAD)?

- **AD** occurs mostly as one or more than one acute, severe complication in patients with a history of previous decompensation. Therefore, it most of the patients it occurs as a further decompensation requiring emergent hospitalization.

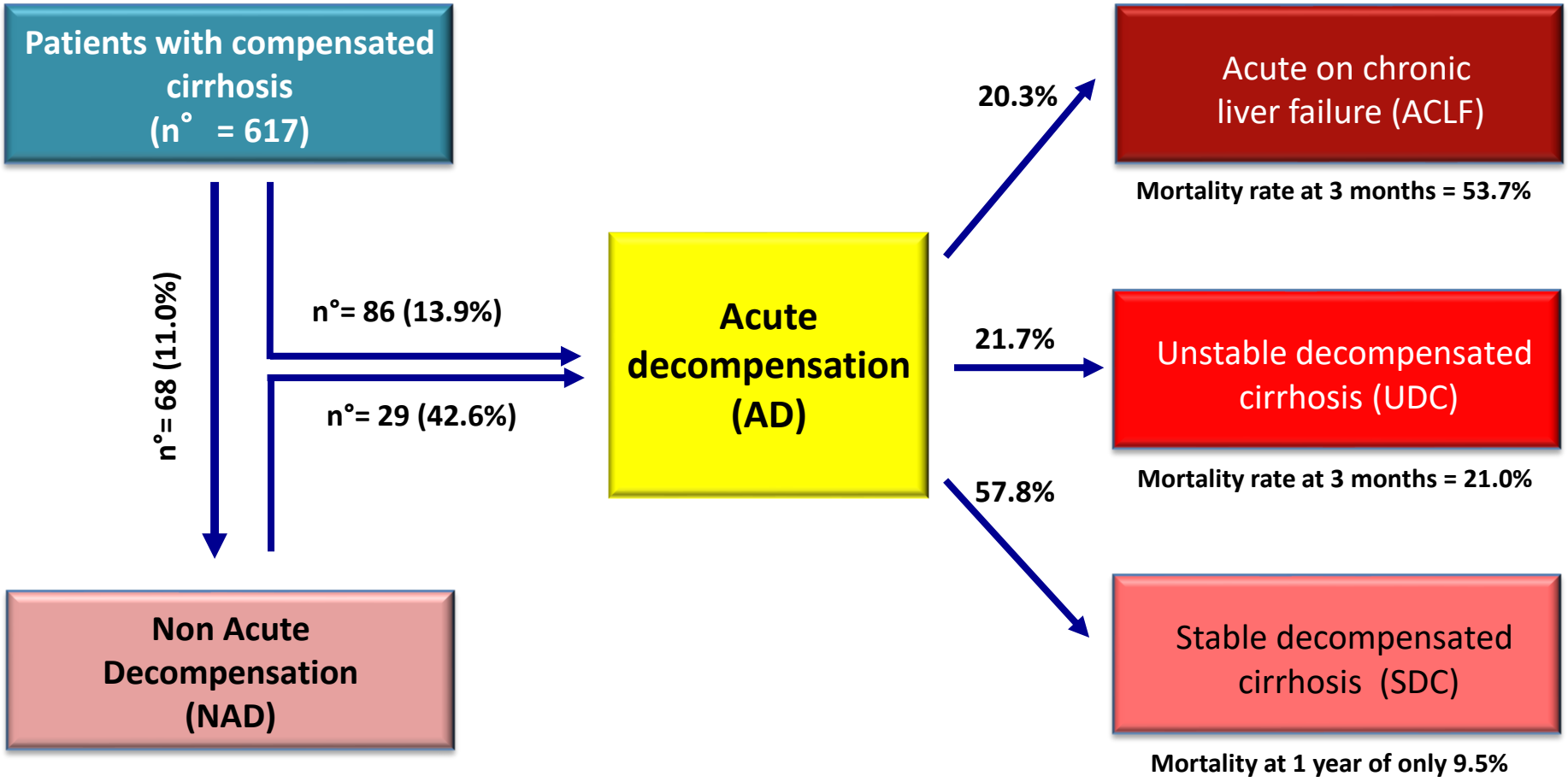
- **NAD** occurs mostly as a single, progressive and mild decompensating event (ascites, encephalopathy) and, usually, does not require hospitalisation.

New definition of decompensation in patients with cirrhosis



Adapted from G. D'Amico et al. J Hepatol. 2022 ; 76 : 202-207

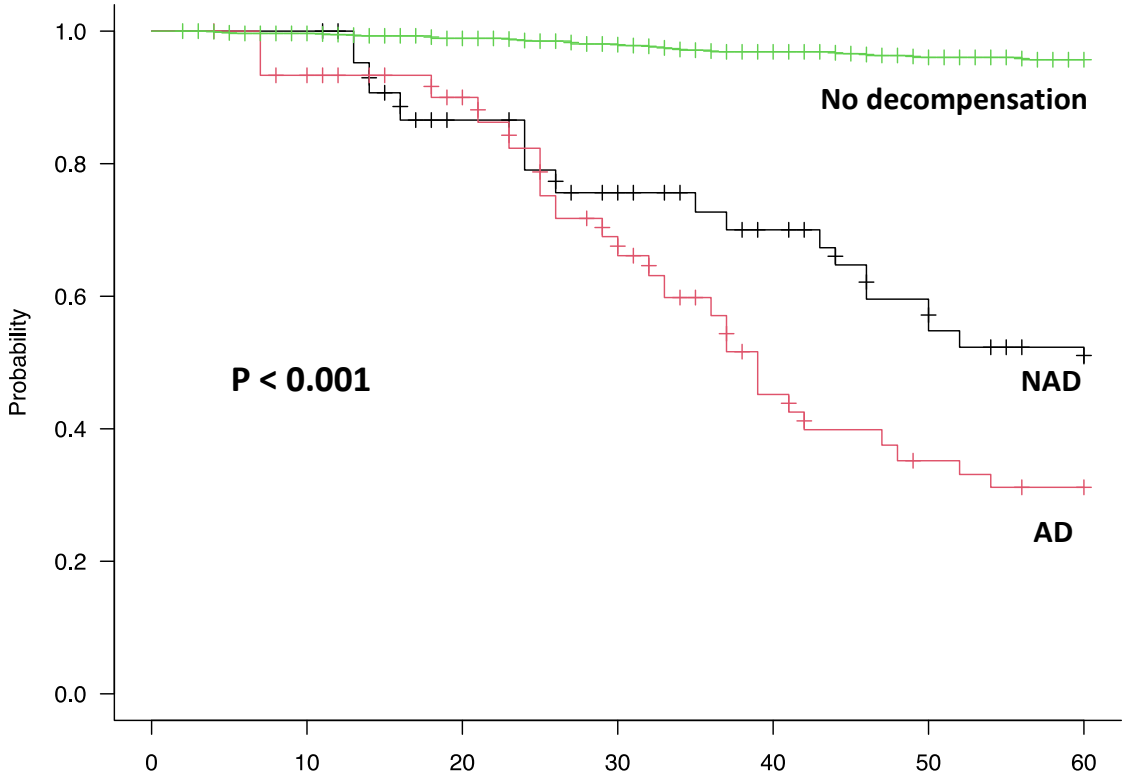
Dynamics and classification of decompensation in patients with cirrhosis



M. Tonon et al. ILC 2022

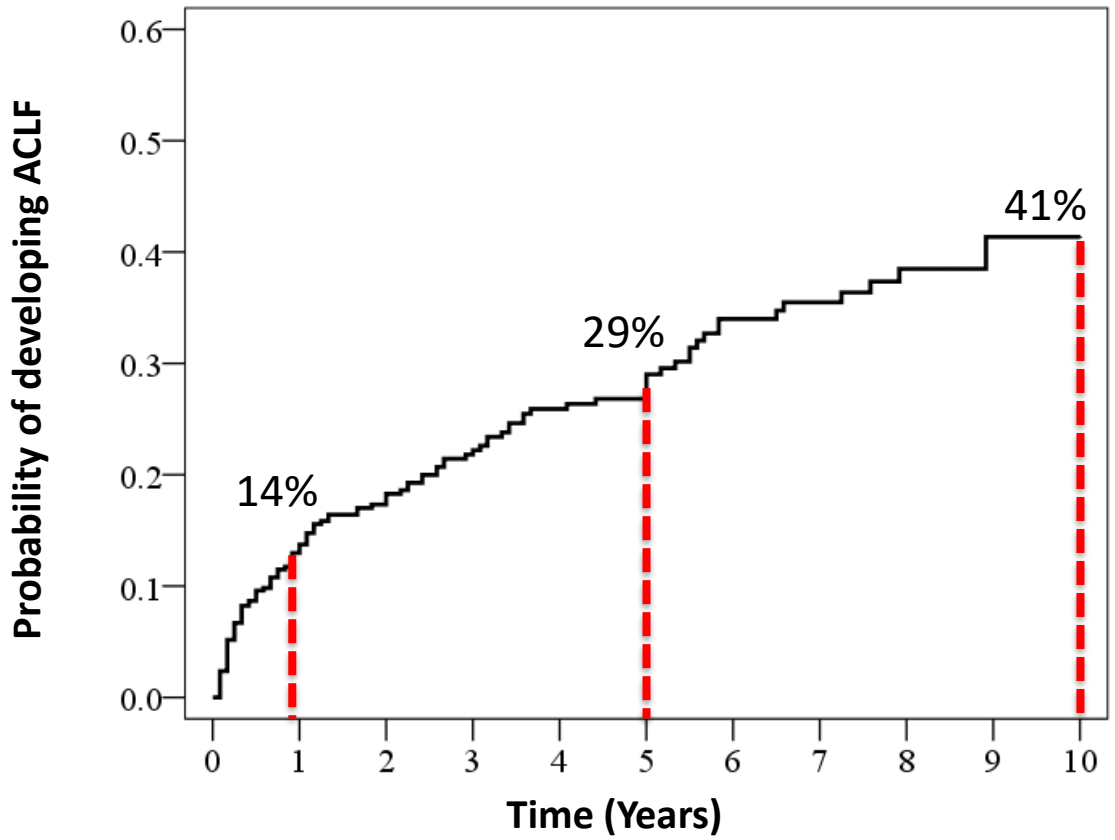
J. Trebicka et al. J. Hepatol. 2020 ; 73 : 842-854

Probability of survival according to the type of decompensation



M. Tonon et al. ILC 2022 (manuscript submitted)

Cumulative probability to develop ACLF in outpatients with cirrhosis



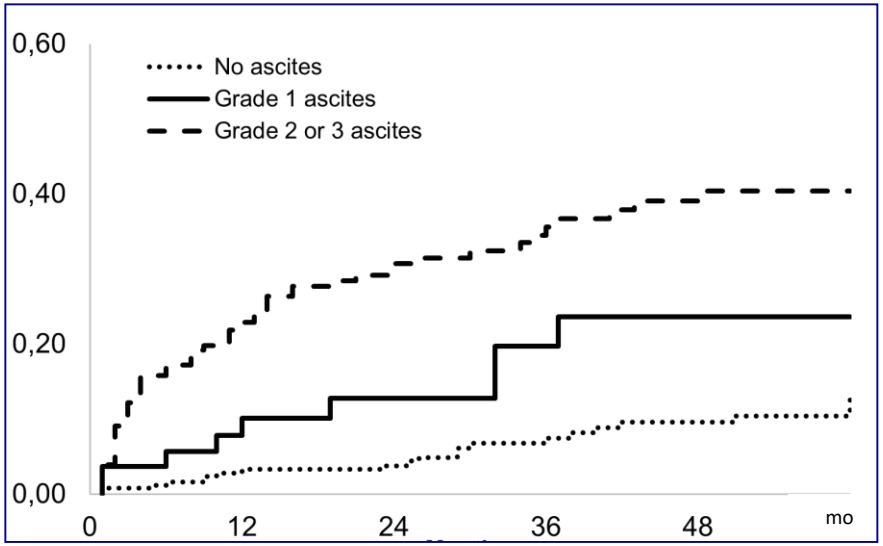
S. Piano et al. J. Hepatol. 2017 ; 67 : 1177-1184

Incidence, predictors and outcome of acute-on-chronic liver failure in outpatients with cirrhosis

Parameter	HR (CI)	P
Presence of ascites	3.00 (0.93-0.99)	0.026
MAP	0.96 (0.01-0.81)	0.005
MELD	1.29 (1.20-1.40)	0.001
Haemoglobin	0.09 (0.01-0.81)	0.032

S. Piano et al. J. Hepatol. 2017 ; 67 : 1177-1184.

Probability to develop ACLF according to the presence and the grade of ascites in patients with cirrhosis

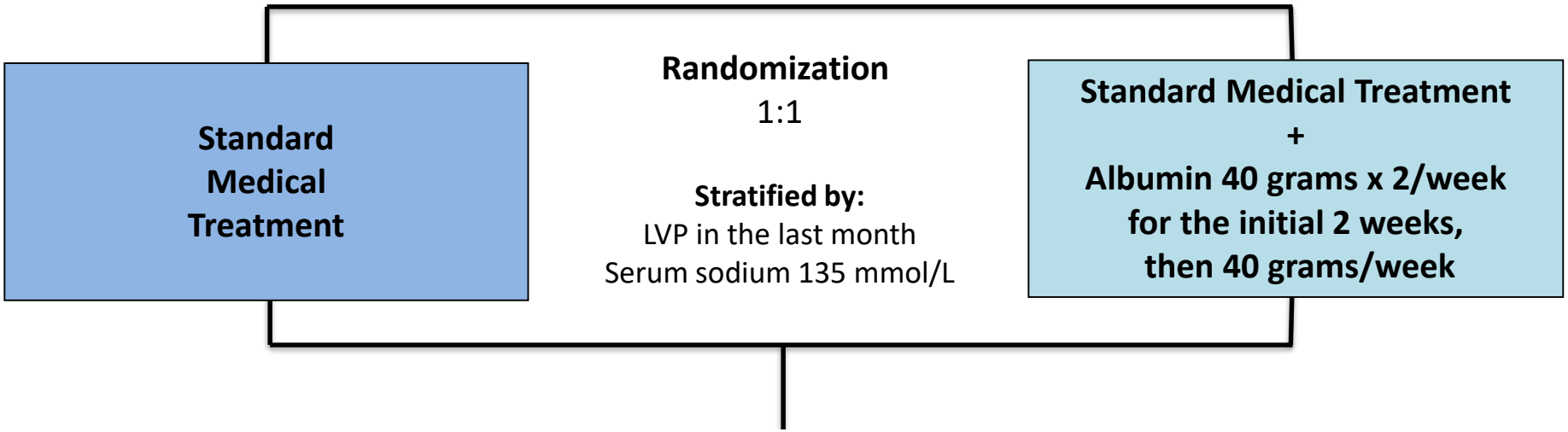


P < 0.001, without ascites vs grade 1; P < 0.038, without ascites vs grade 2 or 3; P < 0.001, grade 1 ascites vs grade 2 or 3

M. Tonon et al. Clin. Gastroenterol. Hepatol. 2021 ; 19 : 358-366

420 Patients with cirrhosis and uncomplicated ascites

ongoing treatment with anti-aldosteronics (≥ 200 mg/day) and furosemide (≥ 25 mg/die)



END OF THE STUDY

Death

TIPS

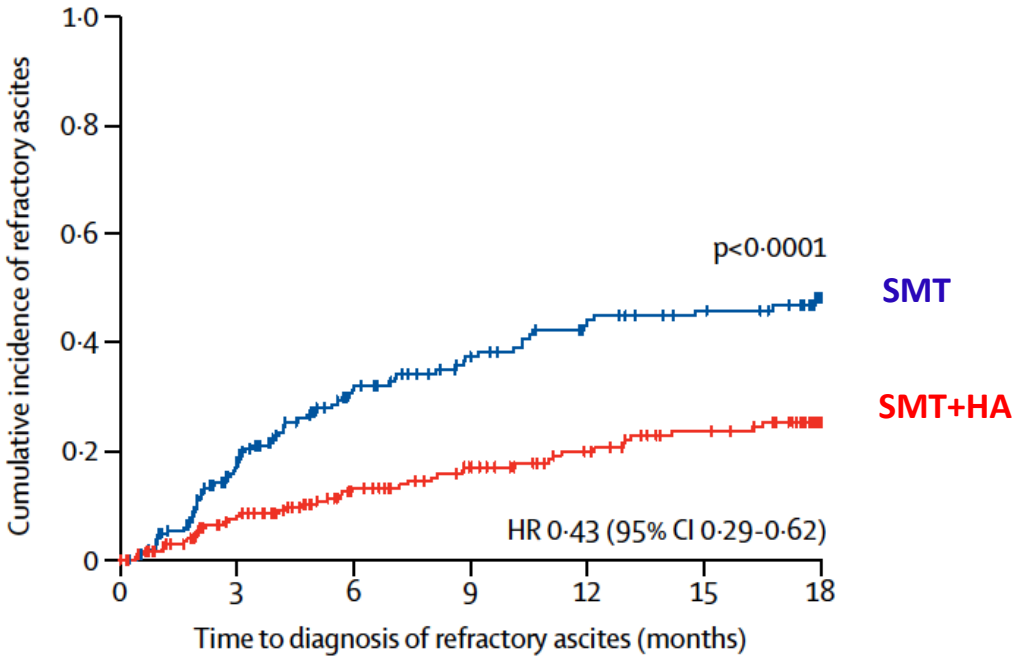
OLT

3 paracentesis/month

Lost follow-up or medical judgment

End follow-up: 18 months

Cumulative incidence of refractory ascites



P. Caraceni et al . Lancet 2018 ; 391 : 2417-2429

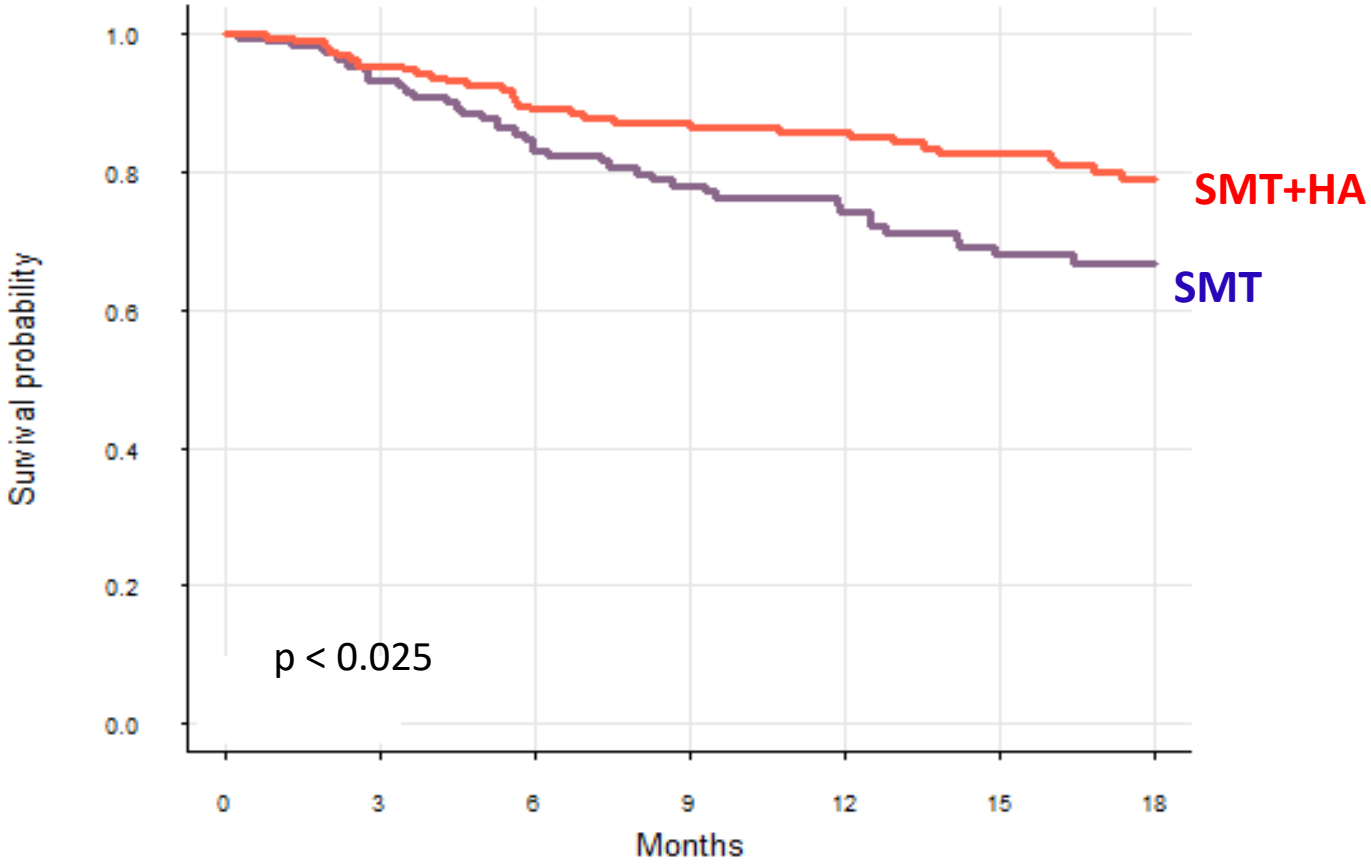
Complications of cirrhosis

CLINICAL EVENT	IRR*	p-value
SBP (diagnosed or suspected)	0.30 (-70%)	<0.001
HE episodes (grade III-IV)	0.47 (-53%)	<0.001
Renal impairment (creatinine >1.5 mg/dl)	0.43 (-57%)	<0.001
Non-SBP bacterial infections	0.74 (-26%)	<0.05
Variceal bleeding	0.98 (-2%)	1.000

**Incidence Rate Ratio (SMT+HA/SMT)*

P. Caraceni et al . Lancet 2018 ; 391 : 2417-2429

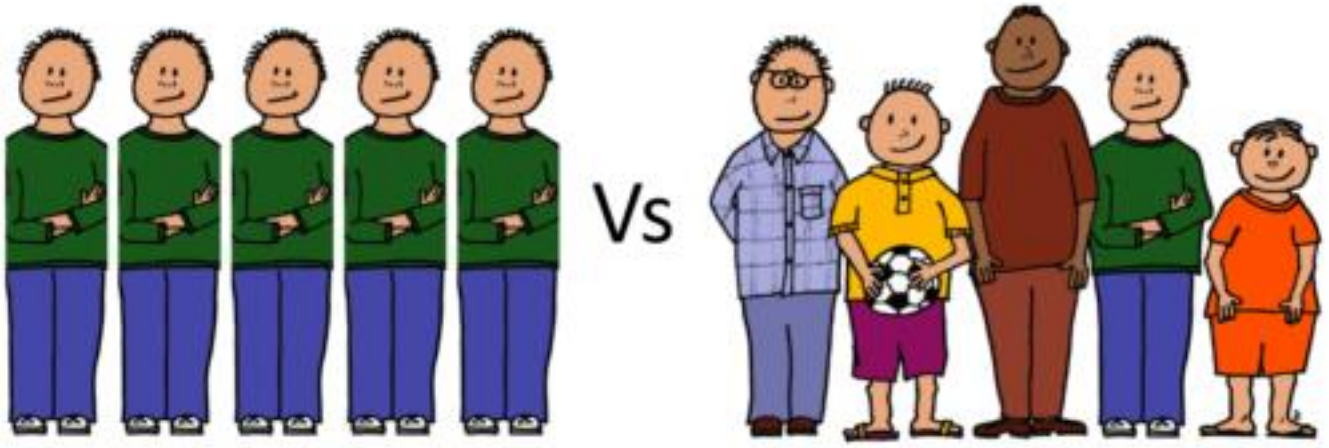
Overall survival



P. Caraceni et al . Lancet 2018 ; 391 : 2417-2429

The Real World Evidence (RWE)

RCTs **RWE**



H.J. Scünemann et al. Res. Synth. Methods 2013 ; 4 : 49-62.

Real world evidence on Long-term Treatment with Human Albumin Solution (LT-HAS) in patients with decompensated cirrhosis

(% Reduction of secondary endpoints)

Secondary endponit	% reduction LT-HAS versus SOC	P
Refractory ascites	- 44.2	< 0.025
SBP	-52.7	< 0.01
HRS	- 62.4	< 0.005
HE	-13.1	N.S.
Hospital admissions	-24.6	< 0.05

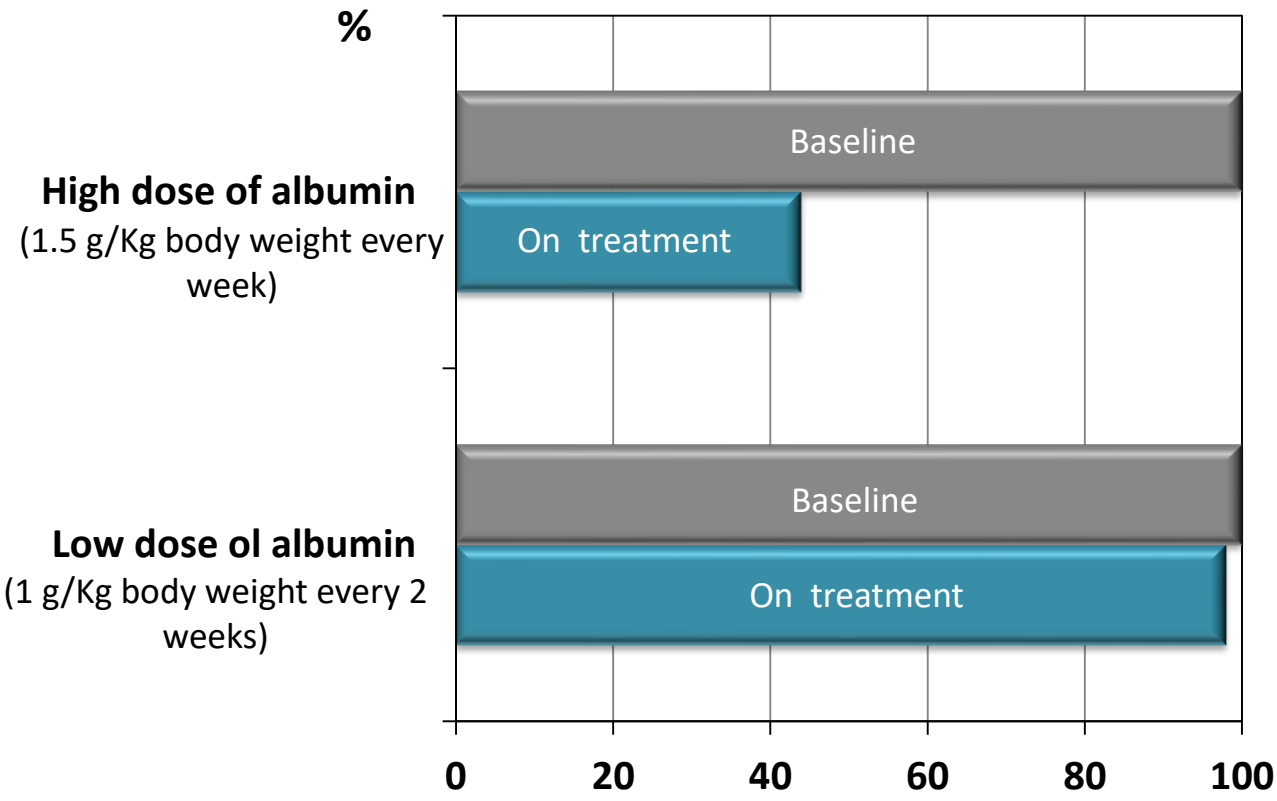
W. Laleman et al. 2023 ; (Abstract presented at EASL meeting)

Prevention of Mortality with Long-Term Administration of Human Albumin in Subjects with acute decompensation and ascites

Primary endpoint

- 12-month transplant free survival

Ratio between the final value and baseline value of serum concentration of IL -6



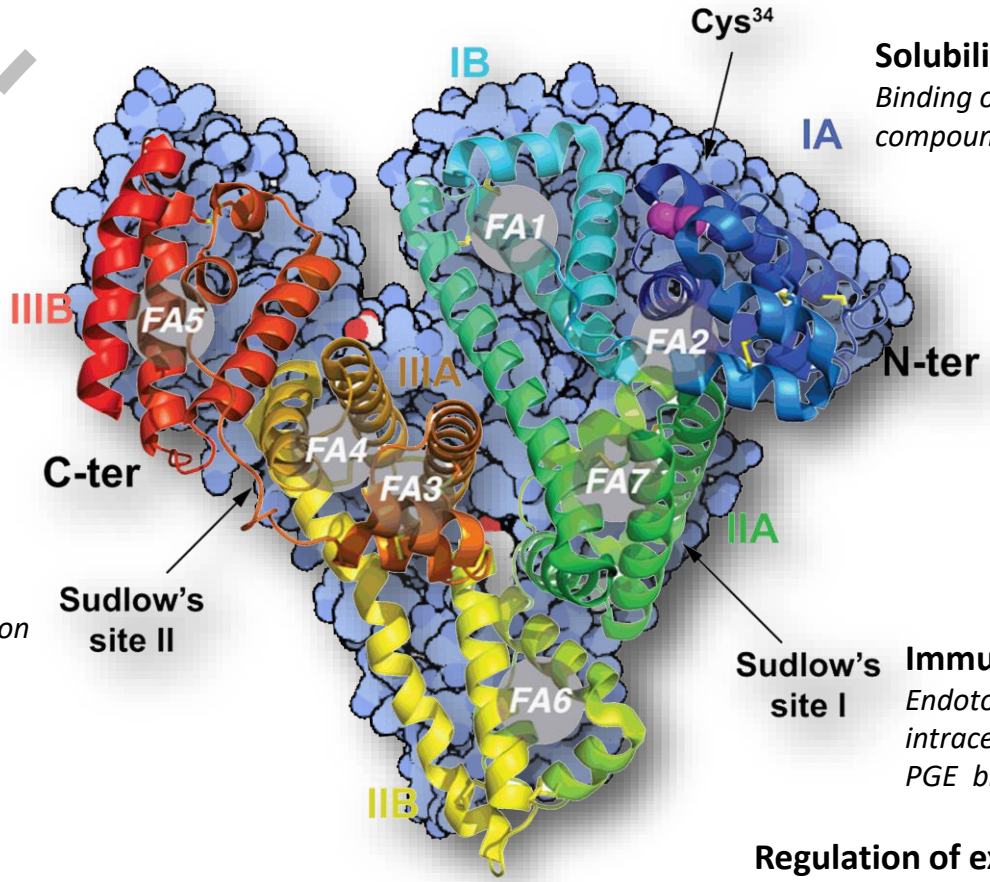
J. Fernandez et al. Gastroenterology 2019 ; 157 : 149-162

Properties of albumin

Oncotic

Regulation of fluid distribution

Negative net charge
High molecular weight
High plasma concentration



Non oncotic

Solubilization and transport
Binding of endogenous and exogenous compounds including drugs

Antioxidant
Free radical and metal ion scavenging

Hemostatic effect
No binding at Cys-34

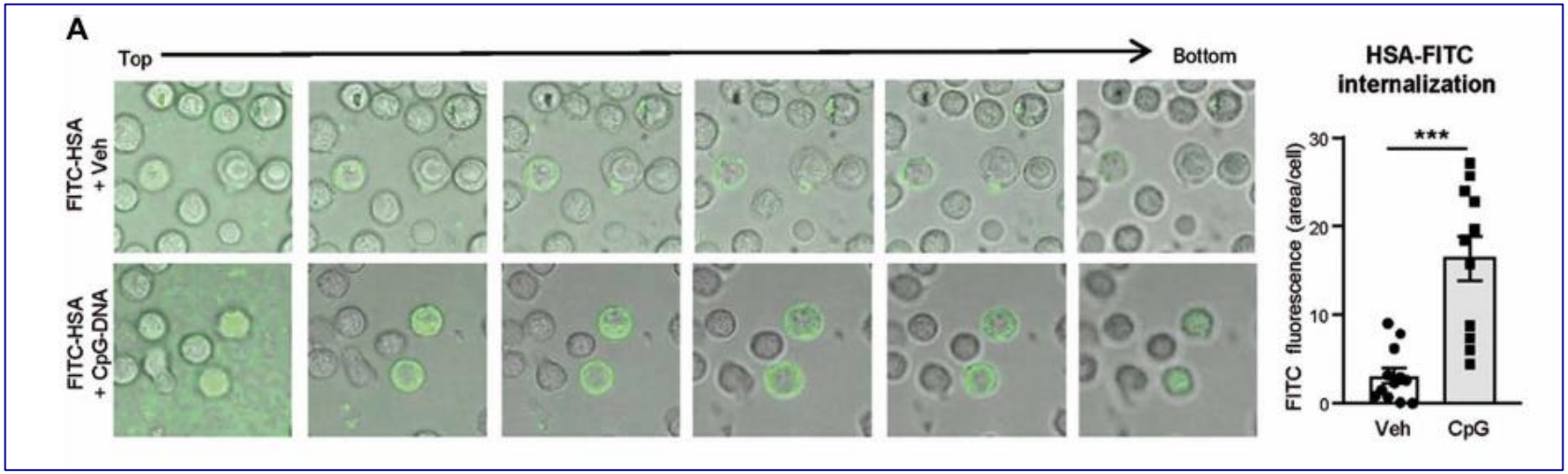
Endothelial stabilization
Immunomodulation and antioxidant properties

Immunomodulation
Endotoxins binding, modulation of intracellular redox state, TNFα inhibition, PGE binding

Regulation of extracellular pH
Binding of H^+

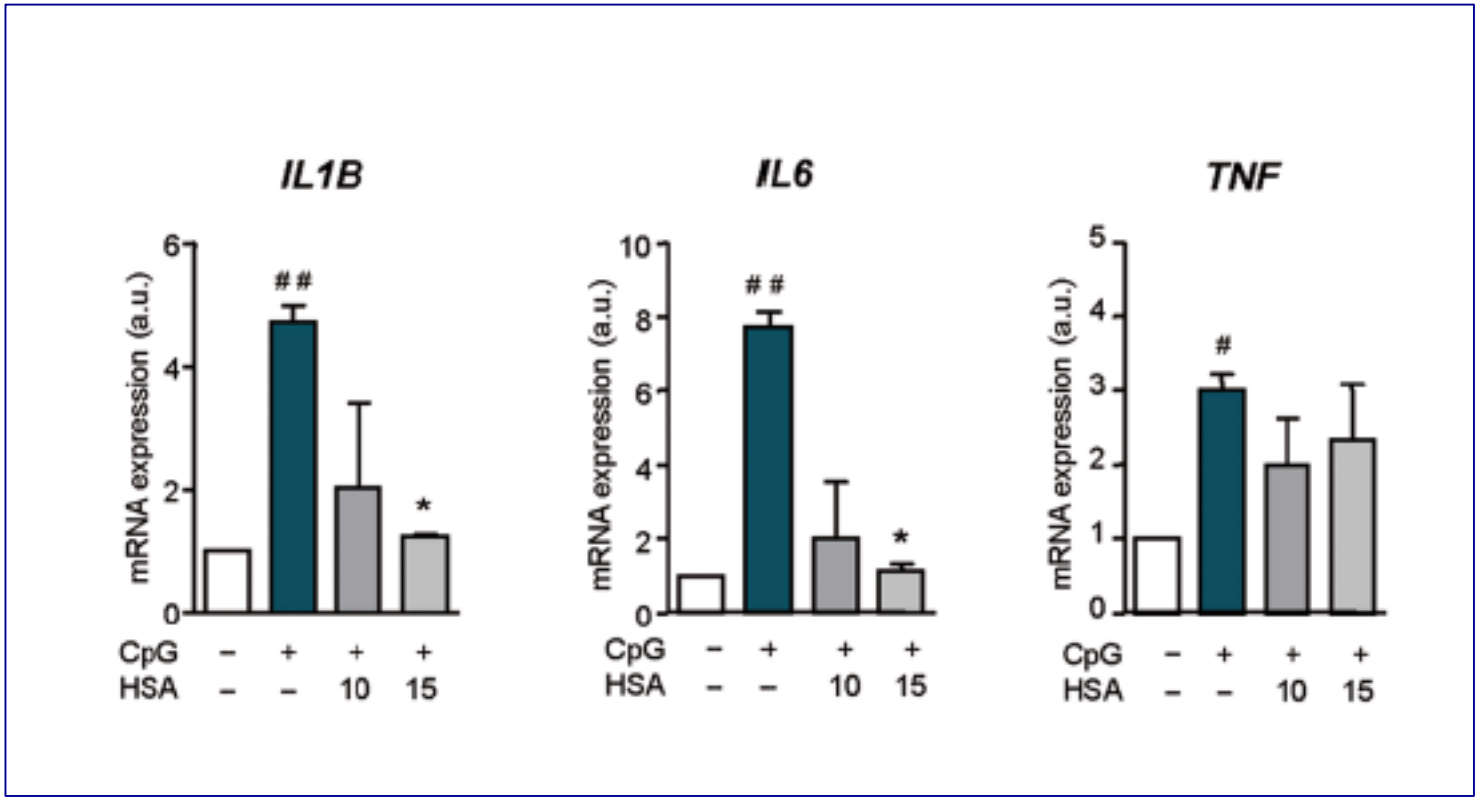
Anti-inflammatory action

Human albumin internalization in leukocytes



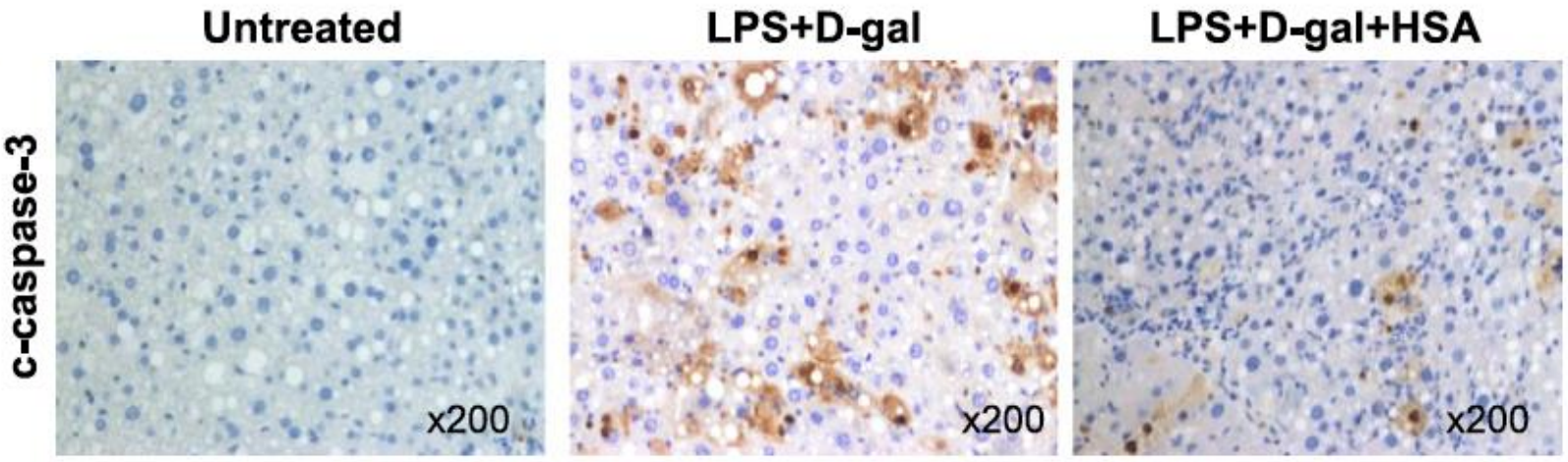
M. Casulleras et al. Sci. Transl. Med. 2020 ; 12 (566) : eaax5135

HAS blocks a DAMP induced cytokine release in leukocytes



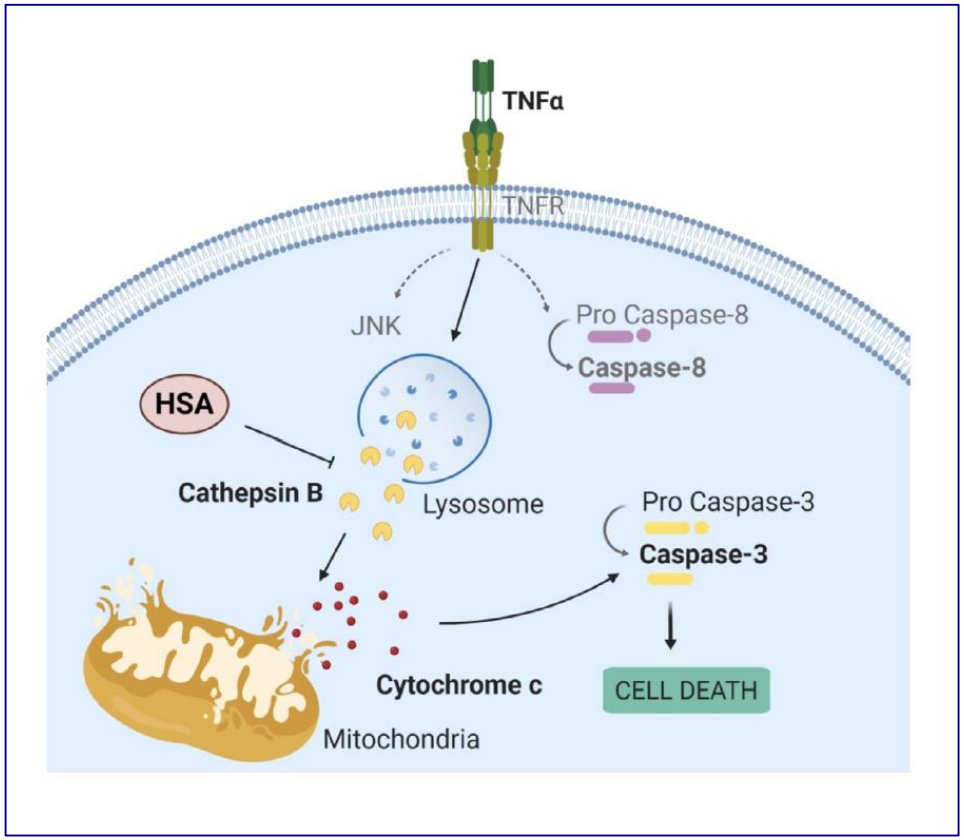
M. Casulleras et al. Sci. Transl. Med. 2020 ; 12 (566) : eaax5135

Cytoprotective effect of Human albumin solution (HAS) on hepatocytes



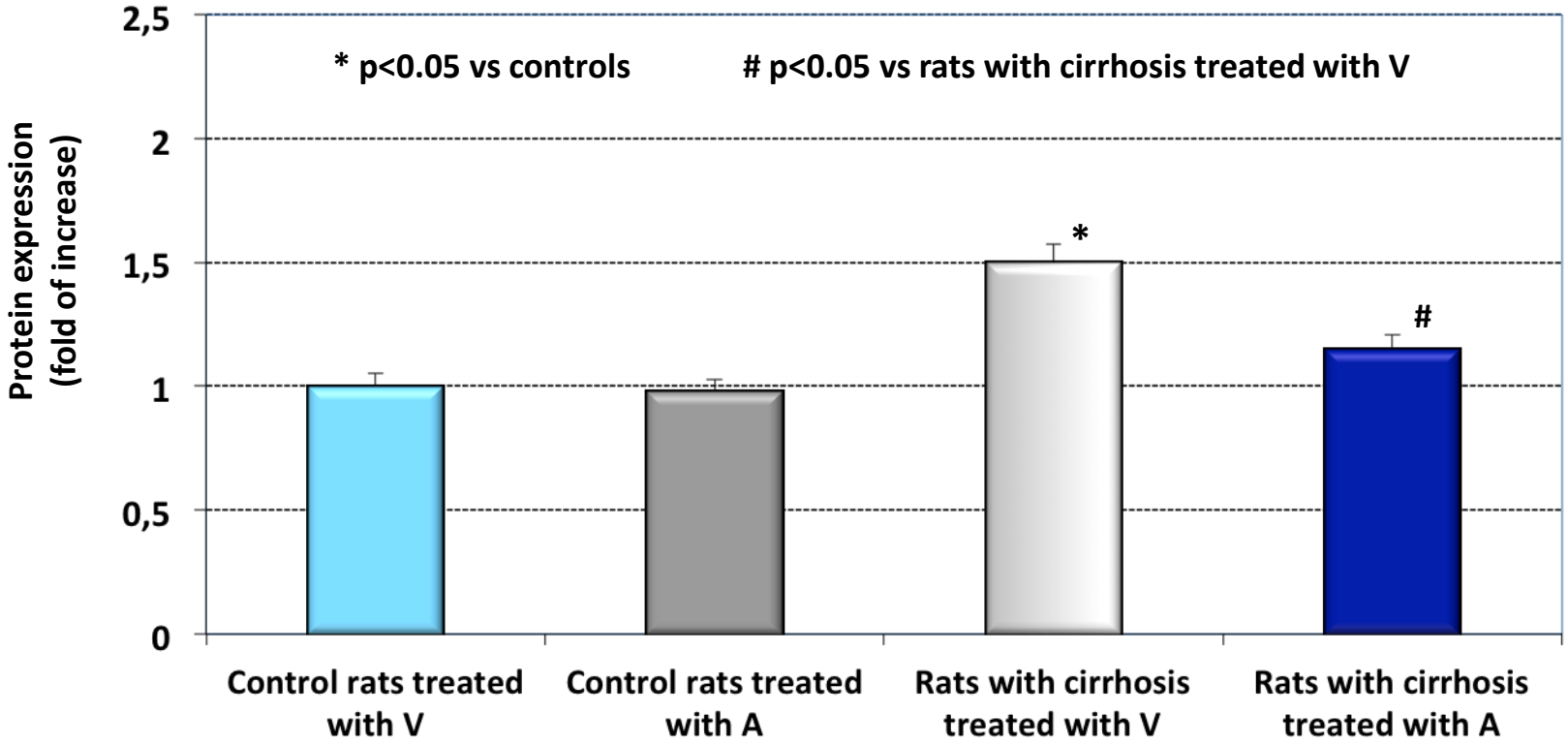
M. Duran-Guell et al. FASEB 2021 ; 35 : e21365

Cytoprotective effect of Human albumin solution (HAS) on hepatocytes



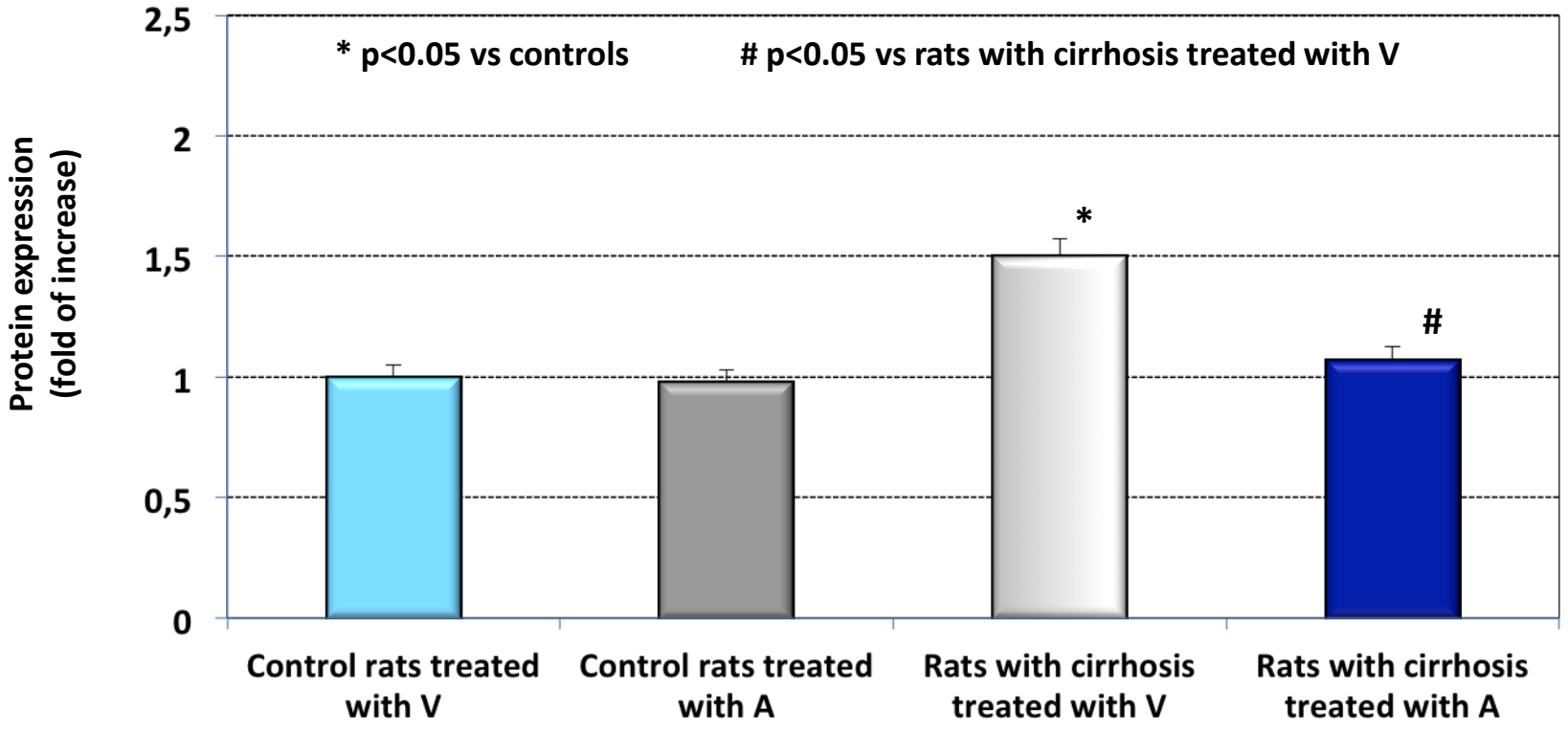
M. Duran-Guell et al. FASEB 2021 ; 35 : e21365

Effects of albumin on TNF-α protein expression in the cardiac tissue according to treatment with vehicle (V) or albumin (A)



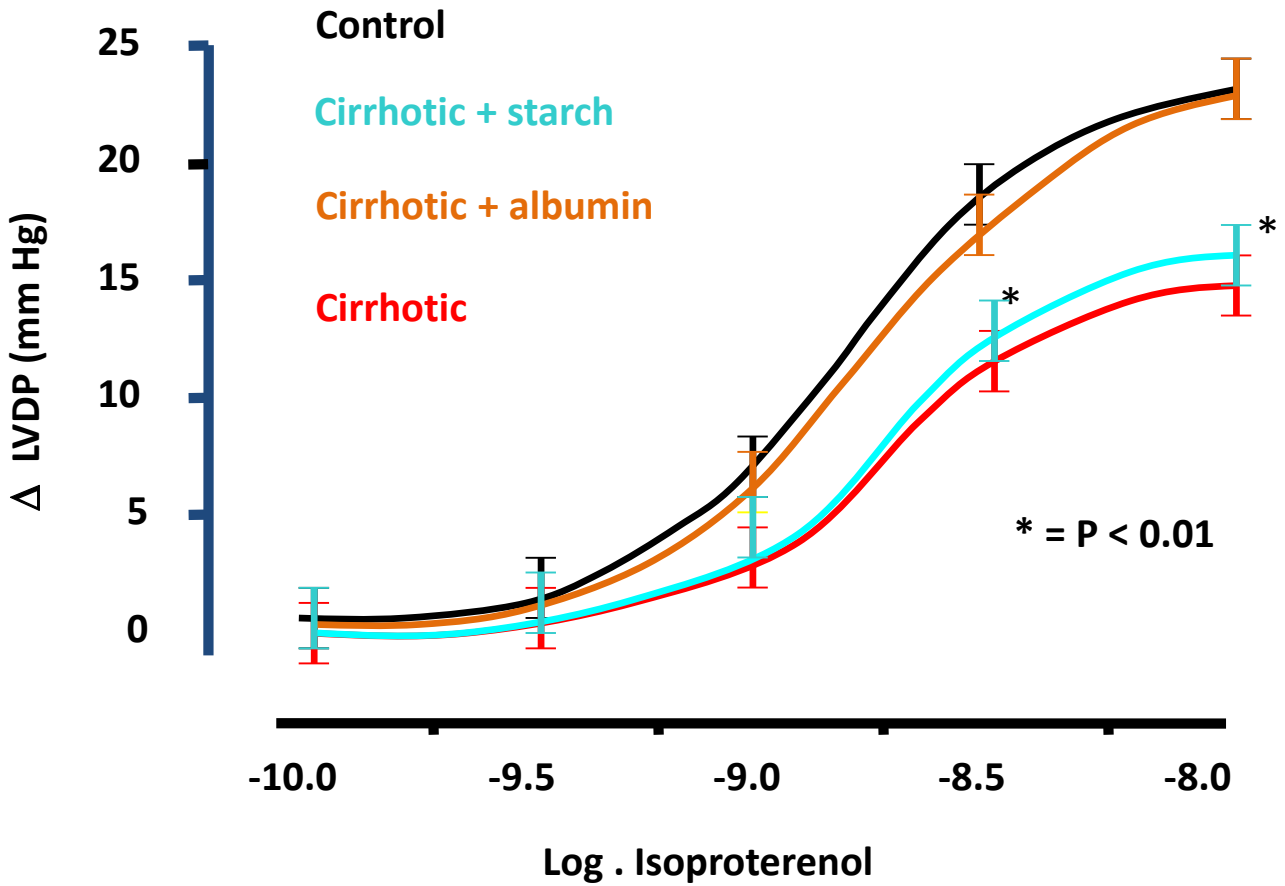
A. Bortoluzzi et al. Hepatology 2013 ; 57 : 266-276

Effects of albumin on iNos protein expression in the cardiac tissue according to treatment with vehicle (V) or albumin (A)



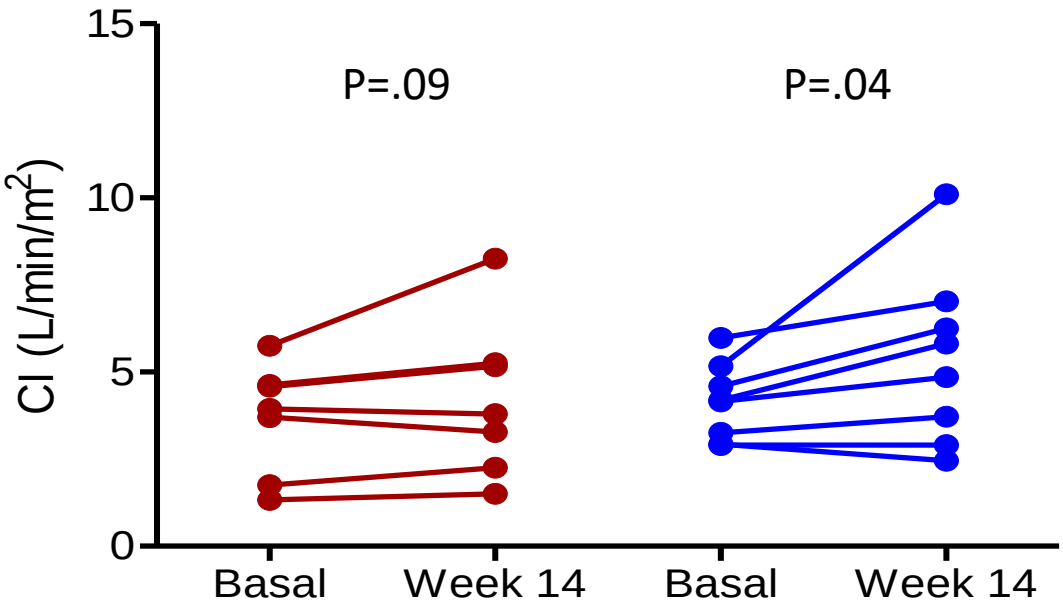
A. Bortoluzzi et al. Hepatology 2013 ; 57 : 266-276

Effects of albumin on cardiac contractility in cirrhotic rats



A. Bortoluzzi et al. Hepatology 2013 ; 57 : 266-276

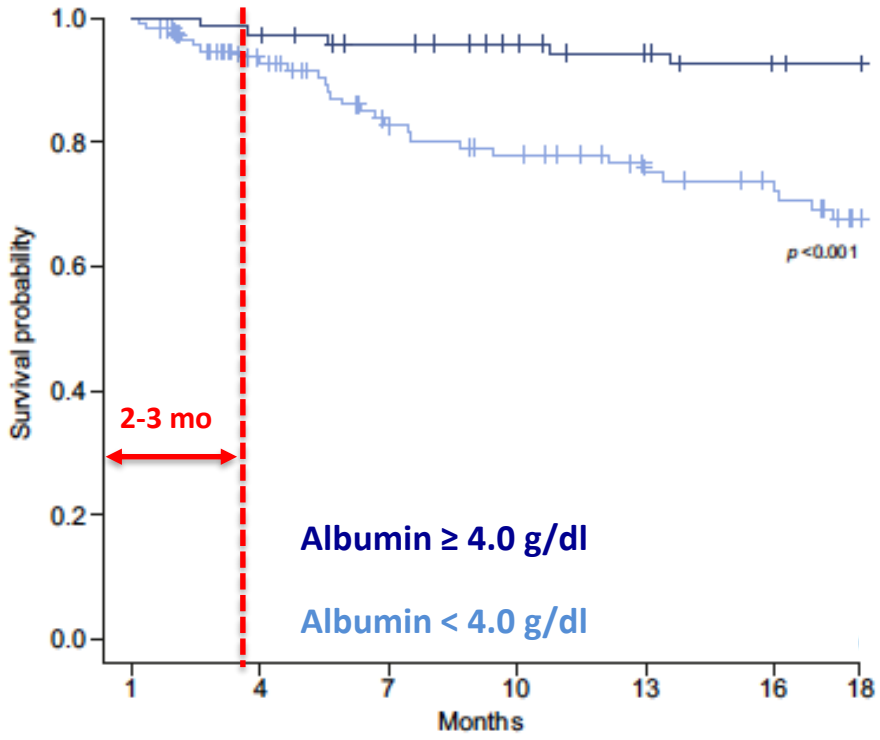
Effects of albumin administration on cardiocirculatory function



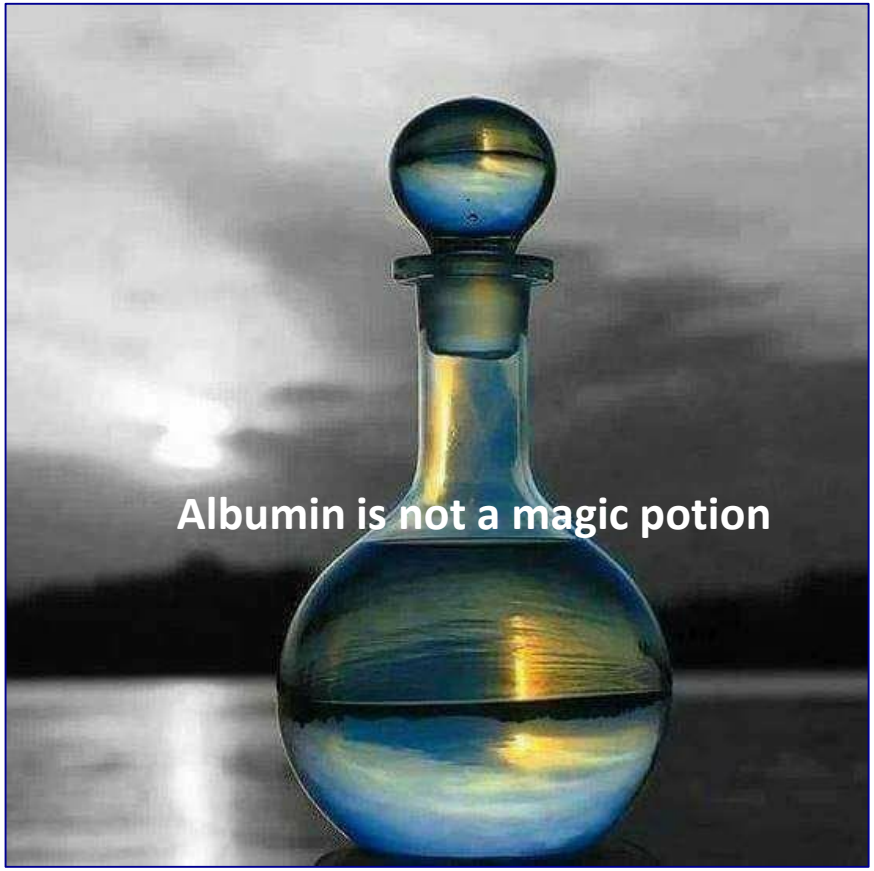
(1 g/Kg body weight every 2 weeks) **(1.5 g/Kg body weight every week)**

J. Fernandez et al. Gastroenterology 2019 ; 157 : 149-162

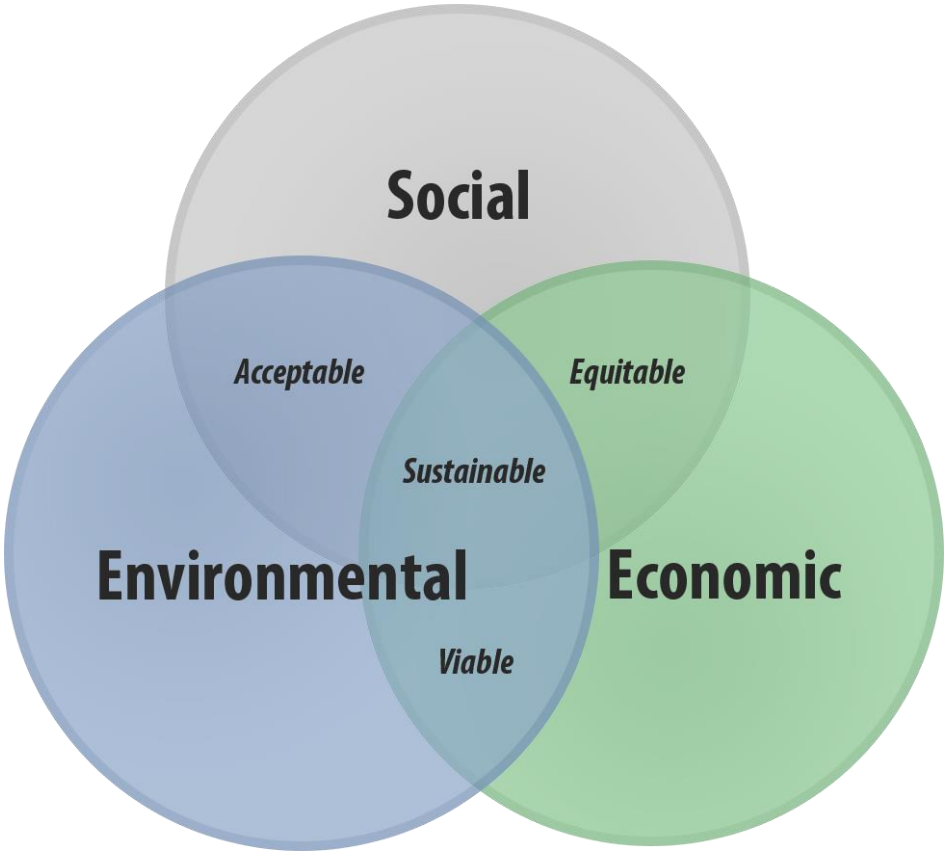
On treatment 1-month serum albumin level and survival



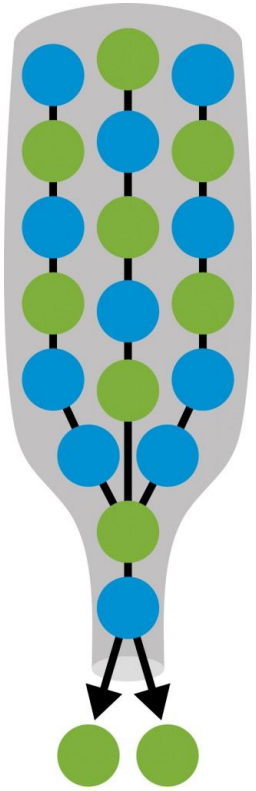
P. Caraceni et al. J. Hepatol. 2021 ; 74 : 340-349


Albumin is not a magic potion

Sustainability of a therapeutic option

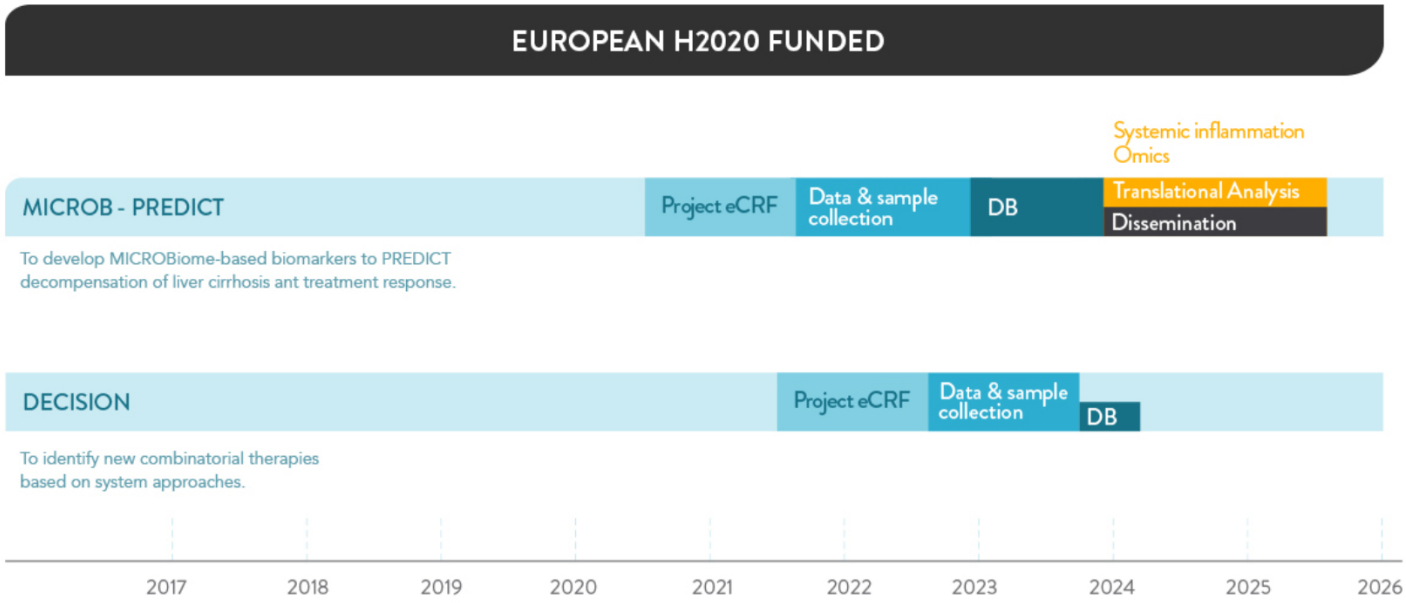


Strategies to implement the use of human albumin in the management of decompensated cirrhosis

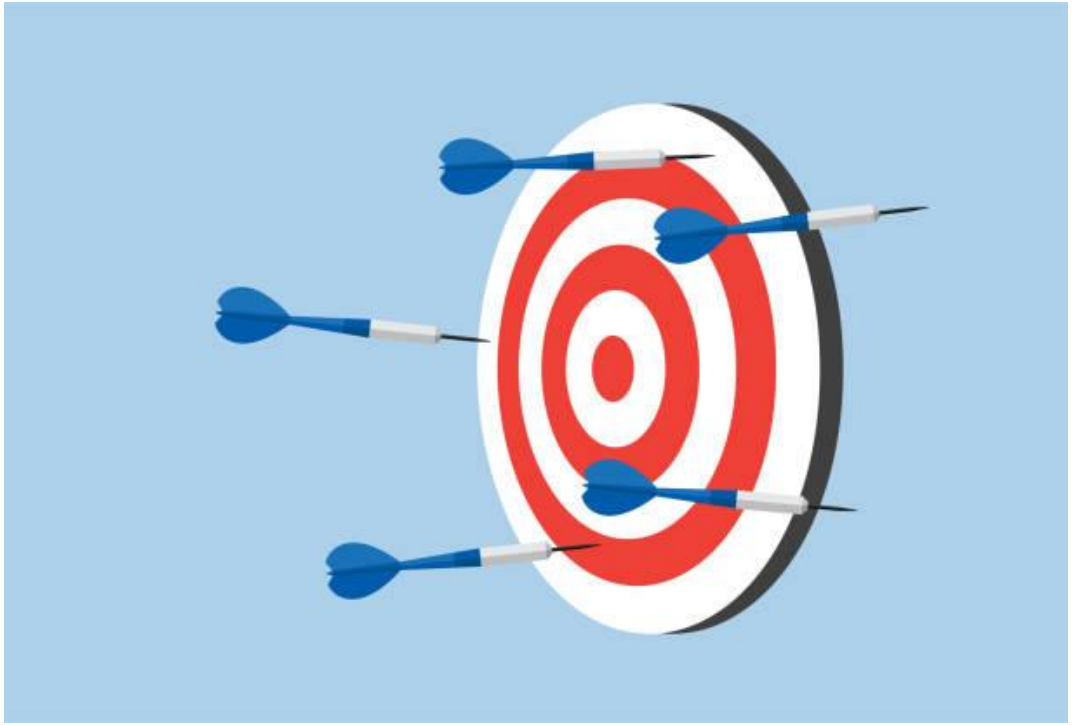


- To be selective in its prescription
- To use it properly
- To remove the logistic barriers for its long-term use
- To investigate how to improve the quality of its solution

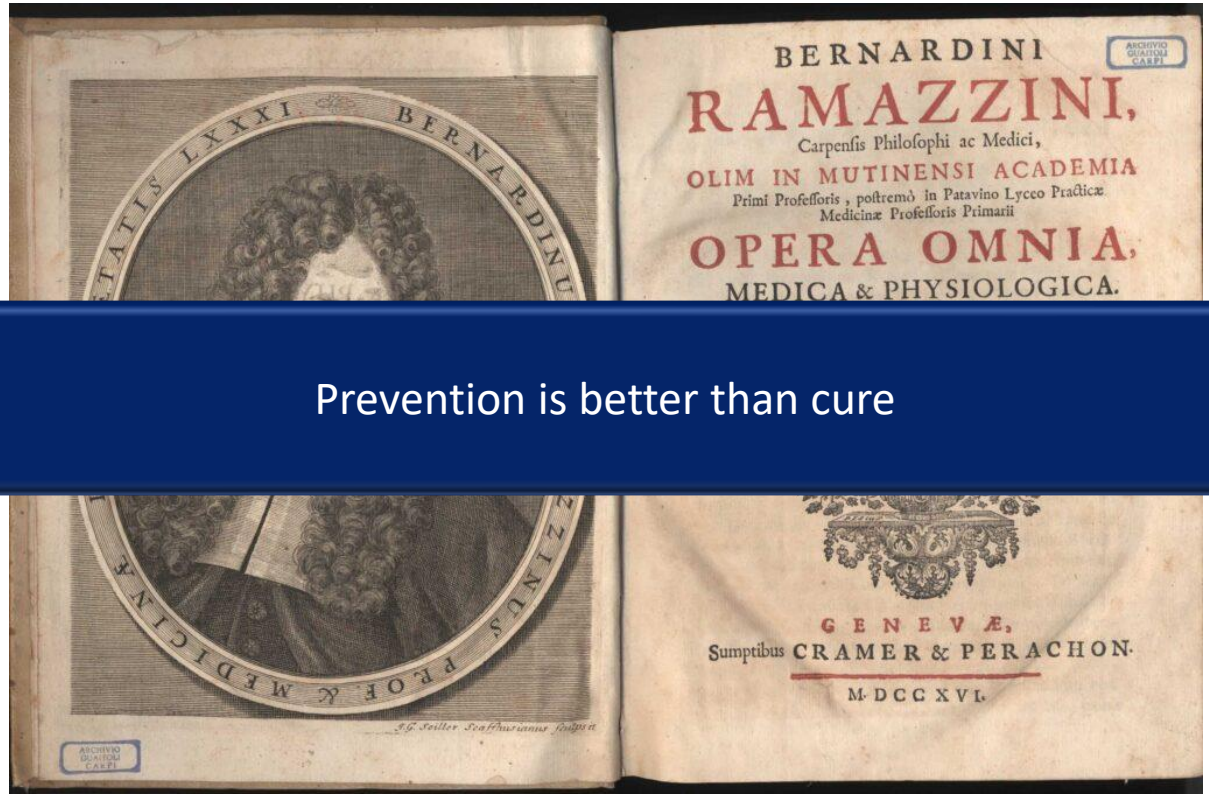
Towards a personalized and precision medicine in patients with decompensated cirrhosis



Prevention of decompensation



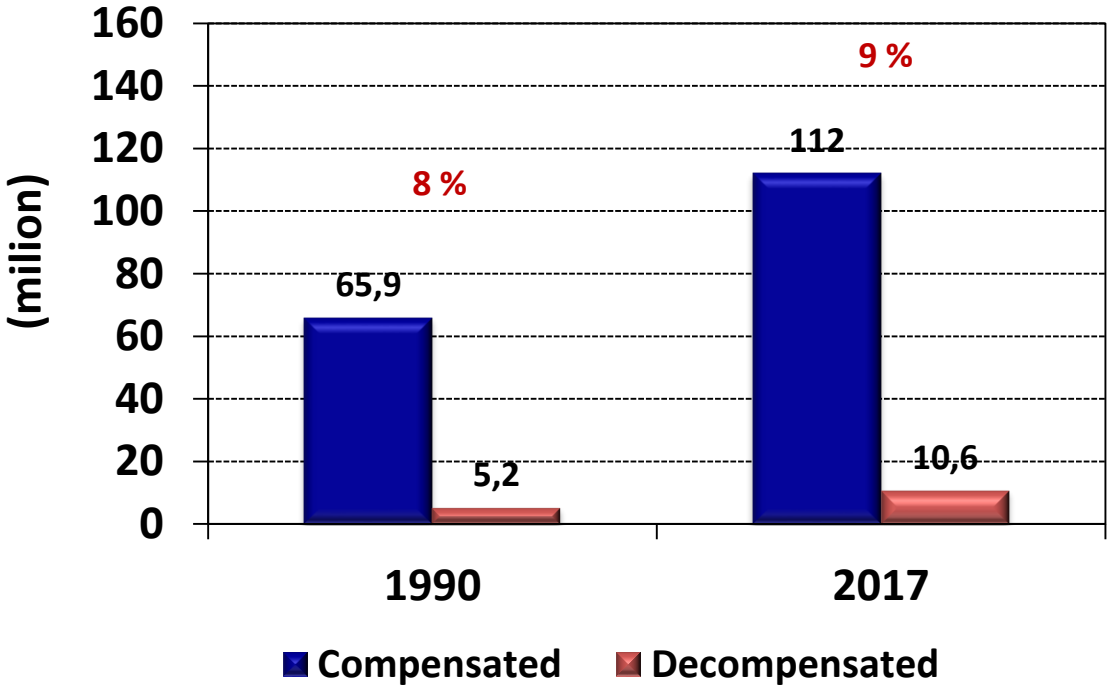
Prevention of decompensation



Prevention is better than cure

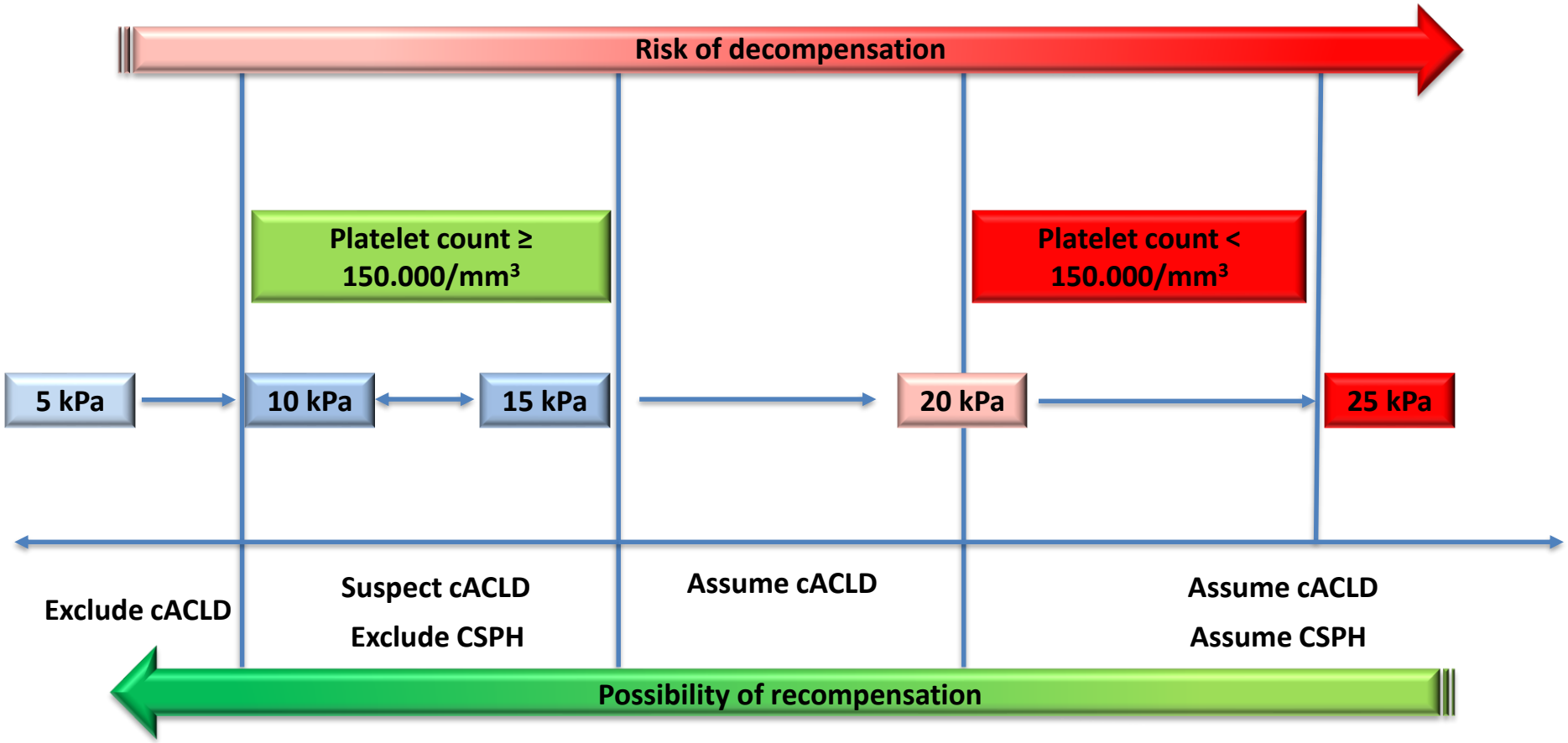
Bernardino Ramazzini (Carpi, 4 ottobre 1633 – Padova, 5 novembre 1714) «Thought developed during the bovine plague of the Venetian Republic in the early eighteenth century»

Number of prevalent cases of compensated and decompensated cirrhosis in 1990 and 2017



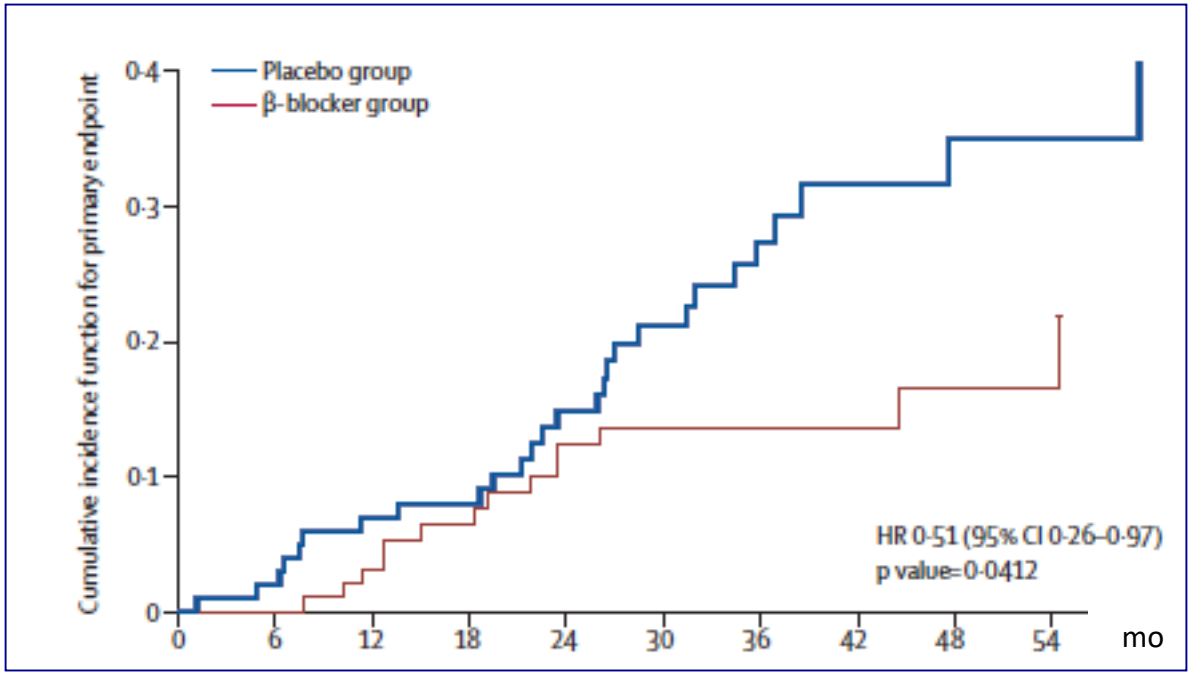
Lancet 2020 ; 5 : 245-266

The role of «FIVE» to identify patients with compensated Advanced Chronic Liver Disease (cACLD) at risk of clinically relevant decompensating events



Adapted from R. De Franchis et al. J. Hepatol. 2022 ; 76 : 959-974

Probability to develop decompensation according to the use of β-blockers in patients with cirrhosis and HVPG ≥ 10 mm Hg



C. Villanueva et al. Lancet 2019 ; 393 : 1597-1608

Prevention of decompensation


THE ELEPHANT IN
the Room

Ancillary unsolved questions

- Should bacterial infection included in the definition of AD or further decompensation or should they be considered always as a precipitating event?
- Should jaundice be included in the definition of decompensation in the majority of published studies. If yes on the basis of which criterion?
- How to define re-compensation?

Bacterial infections in cirrhosis: Precipitating factor or decompensating event?

Piano S. et al. Clin Liver Dis. 2021 ; 25 : 357-372

How can we define a decompensating event in patients with cirrhosis?

A complication that occurs with an high prevalence
during the course of the disease with a strong link to its pathophysiology
and a negative prognostic effect.

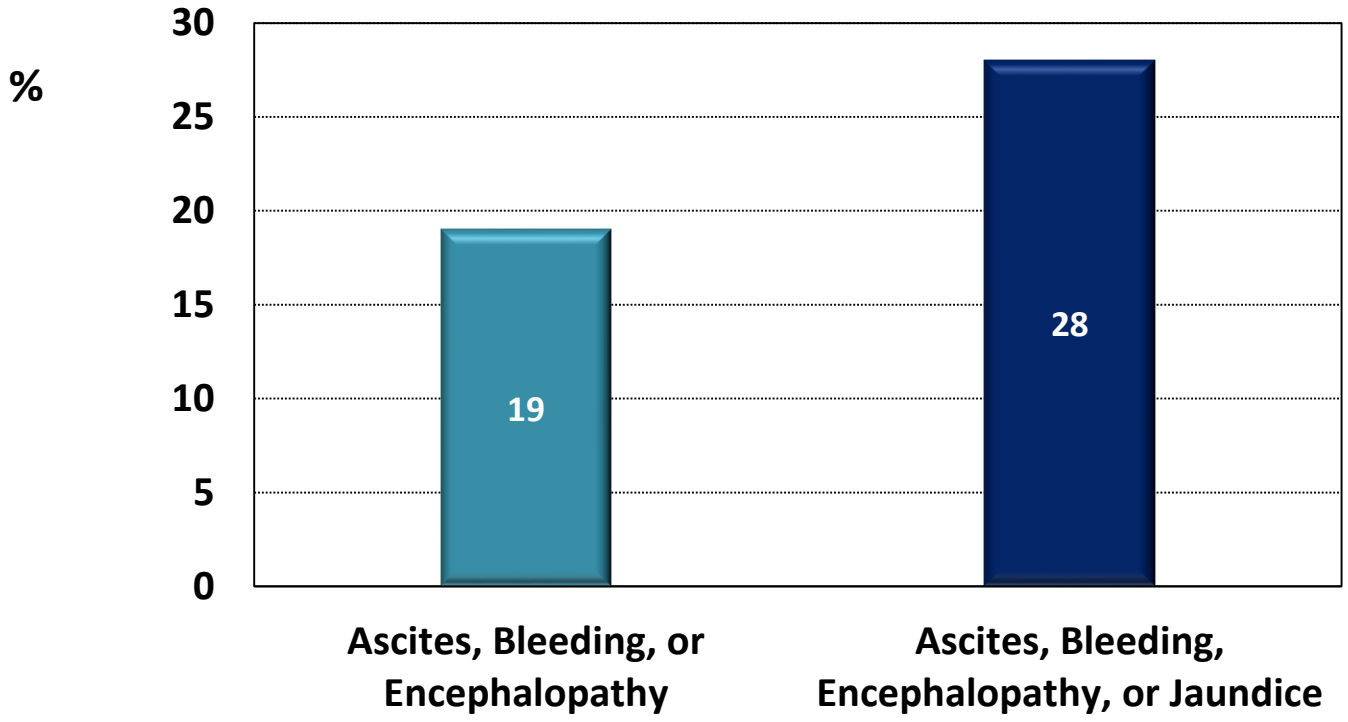
Major complications in cirrhosis

- Ascites
- Hepatic encephalopathy
- Gastrointestinal bleeding
- Extrahepatic organ or system failure/dysfunction
- Jaundice
- HCC
- Bacterial infections
- Sarcopenia
- Osteoporosis

The historically composited definition of decompensated cirrhosis

Definition of decompensation	N°
Development of Ascites, Bleeding, or Encephalopathy	42
Development of Ascites, Bleeding, Encephalopathy, or Jaundice	31
Any combination of Ascites, Bleeding, Encephalopathy, or Jaundice with HCC	13
Any combination of Ascites, Bleeding, Encephalopathy, or Jaudice in an increase of CTP score ≥ 2	9
Any combination of Ascites, Bleeding, Encephalopathy, or Jaundice with an increase in INR, or development of varices, or need of diuretics	9

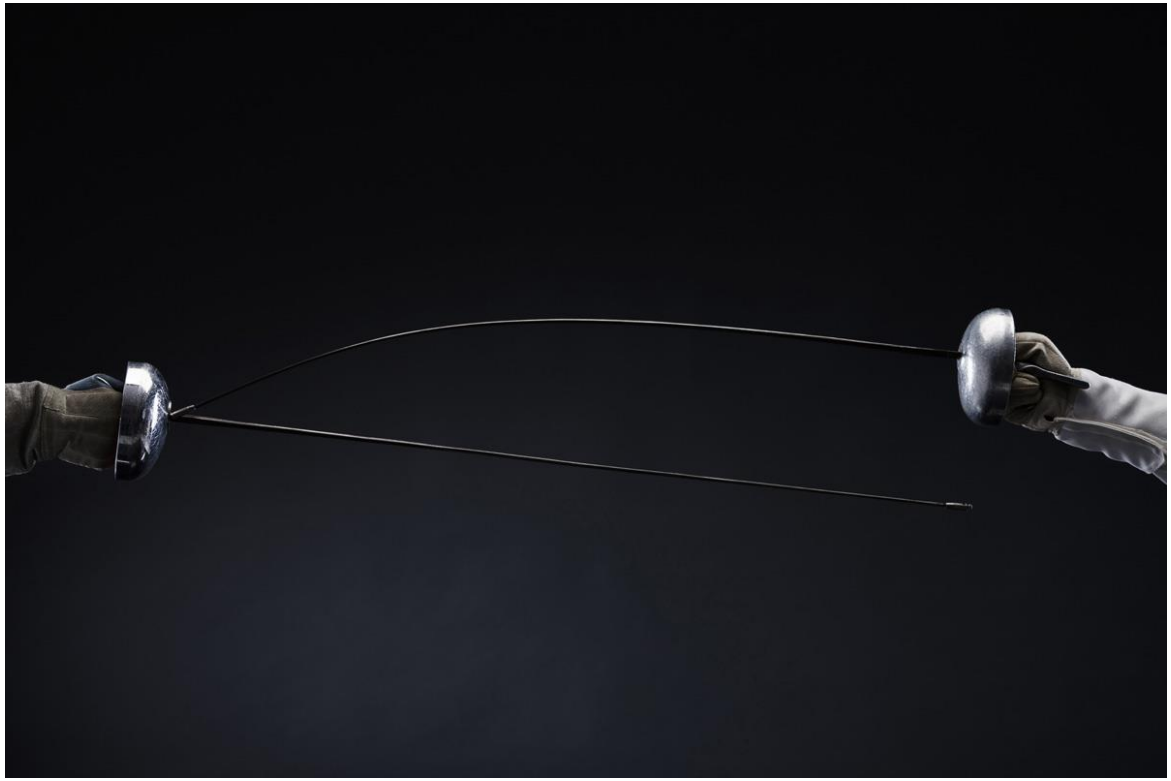
Five year incidence rate of decompensation according to the definition



Feature of well-standardized decompensating events in cirrhosis

	High relative prevalence	Absolute specificity	Negative impact on prognosis	Link to pathophysiology
Ascites	Yes	No	Yes	Yes
Variceal bleeding	Yes	No	Yes	Yes
Hepatic encephalopathy	Yes	No	Yes	Yes
Jaundice	Yes	No	Yes	Yes

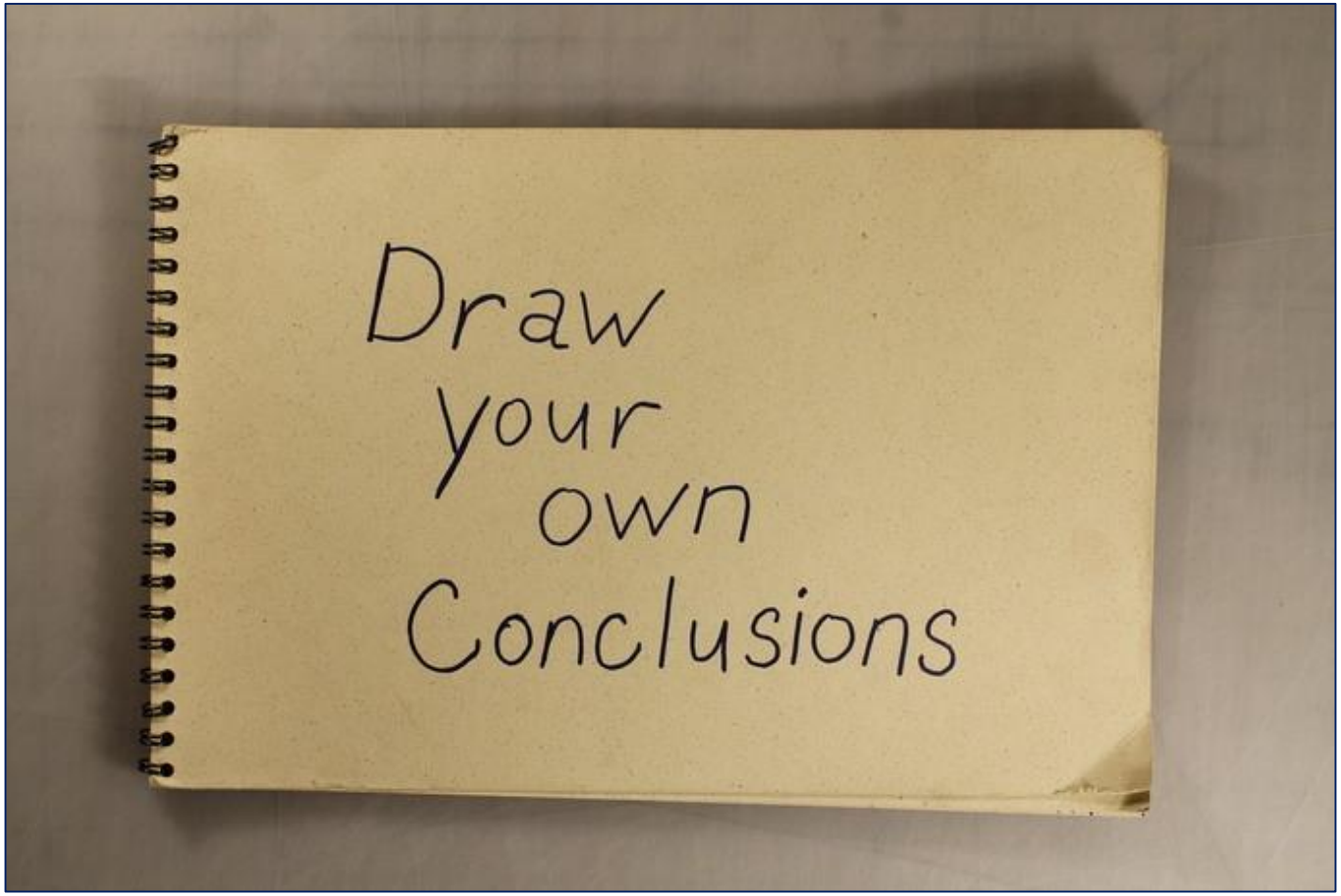
An evaluation in the tip of foil



Feature of bacterial infections in cirrhosis

	High relative prevalence	Absolute specificity	Negative impact on prognosis	Link to pathophysiology
Ascites	Yes	No	Yes	Yes
Variceal bleeding	Yes	No	Yes	Yes
Hepatic encephalopathy	Yes	No	Yes	Yes
Jaundice	Yes	No	Yes	Yes
Bacterial infections	Yes	No*	Yes	Yes*

- = with the exception of SBP
- = particularly true for SBP


Draw
your
own
Conclusions

Take away messages

- Portal hypertension, systemic inflammation, and oxidative state, concur in the pathogenesis of decompensation and development of organ or system dysfunction/failure in patients with cirrhosis.
- Two patterns of decompensation may occur in patients with cirrhosis: non acute decompensation (NAD) and acute decompensation (AD).
- More than fourty percent of the patients who developed NAD then develop AD.
- In patients with NAD, the long-term use of human albumin solution can prevent AD and ACLF improving survival, and quality of life.
- Although, the beneficial effects of human albumin have been traditionally attributed to plasma volume expansion, they could also be related to its effects modulating systemic and organ inflammation.
- More updated preventive strategies for decompensation should be developed.