Definition and Diagnostic Criteria of Acute Decompensation, Non-Acute Decompensation, and ACLF in Patients with Cirrhosis

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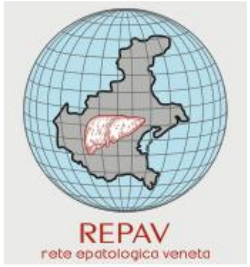


INEDSYS Hepatology Club
4th October 2025, US

Disclosures

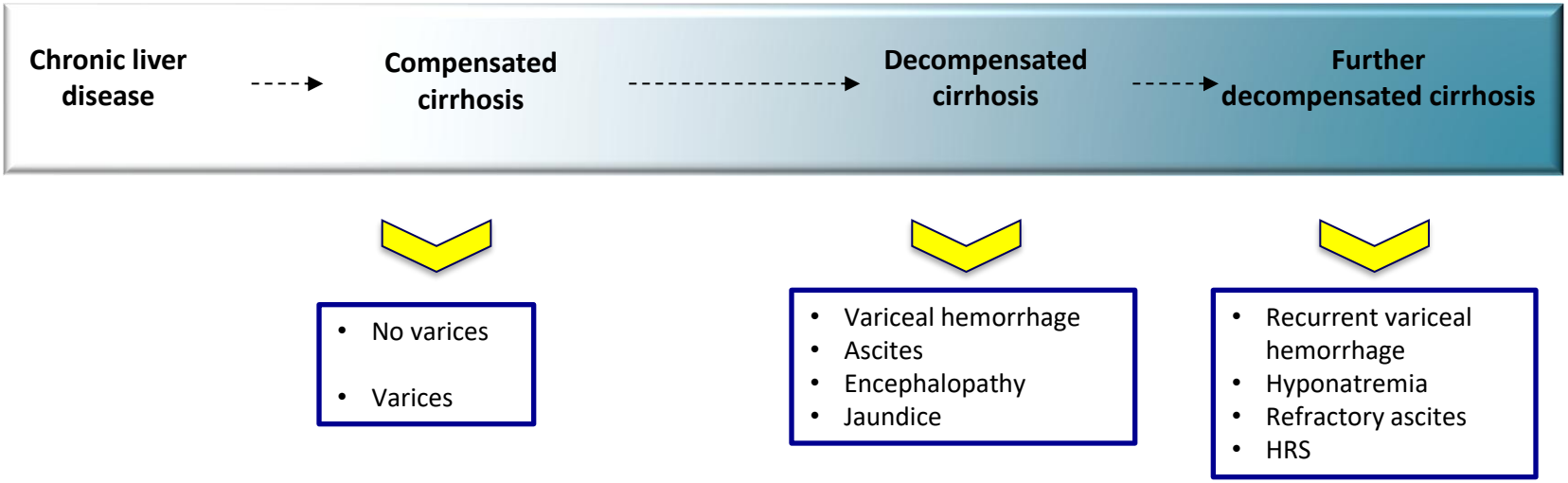
- 2016-2025: Biovie; Advisory Board and patent
- 2014-2021: Bhering; Speaker invitation and travel grant
- 2018-2025: Grifols; Speaker invitation
- 2021-2024: Kedrion; Speaker invitation
- 2021-2023: Biomarin ; Advisory Board

Agenda

- Pathophysiology of decompensation and organ failures
- Definition of decompensation
- Different phenotypes of decompensation

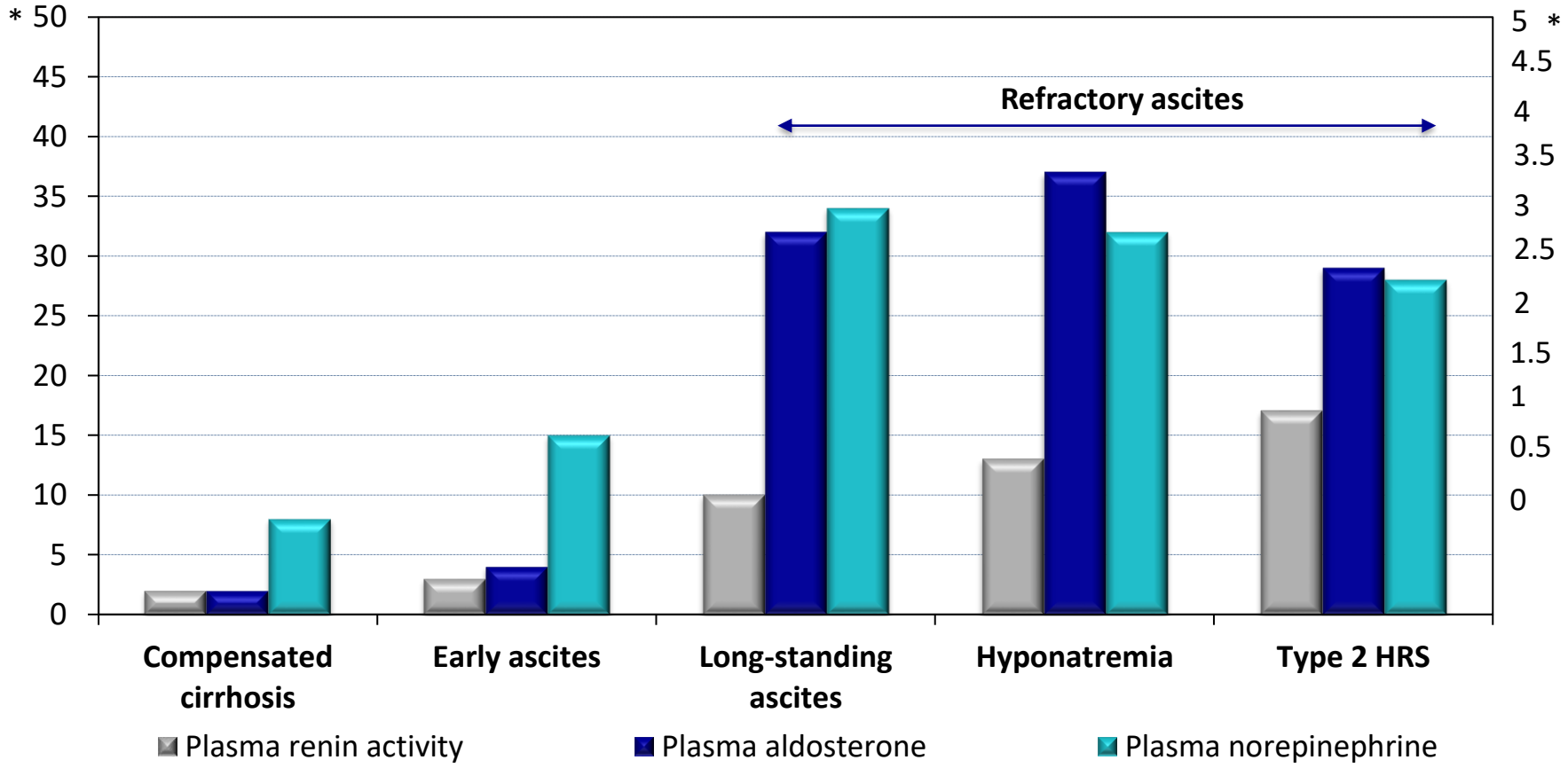
Natural history of cirrhosis

Liver fibrosis	⇧ Portal pressure ⇧ Hyperdynamic circulation ⇧ Activation of endogenous vasoconstrictor factors	⇧⇧ Portal pressure ⇧⇧ Hyperdynamic circulation ⇧⇧ Activation of endogenous vasoconstrictor factors	⇧⇧⇧ Portal pressure ⇧⇧ ⇧ Hyperdynamic circulation ⇧⇧ ⇧ Activation of endogenous vasoconstrictor factors



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

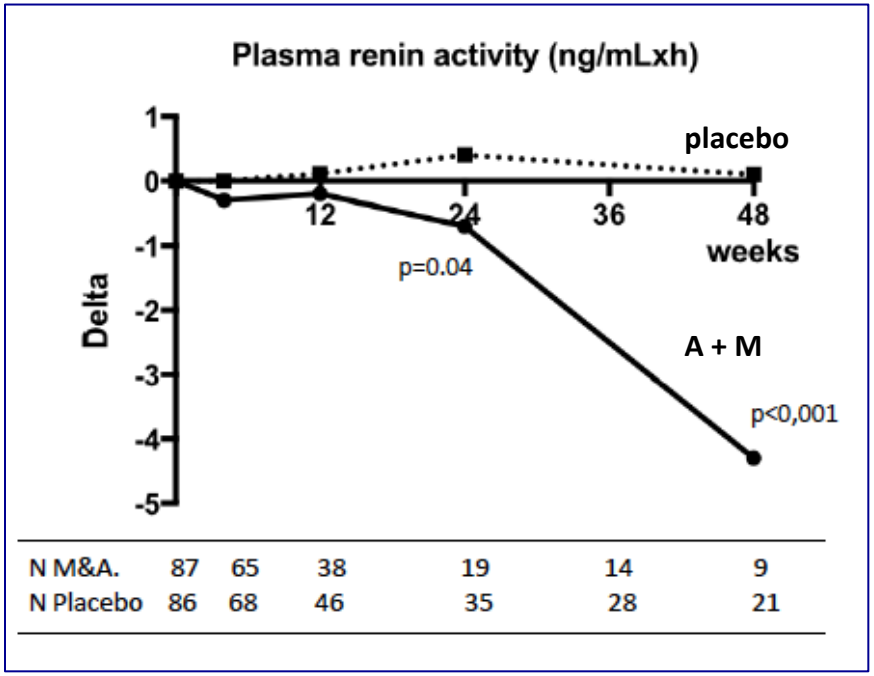
Increase in endogenous systemic vasoactive and sodium-retaining molecules in cirrhosis

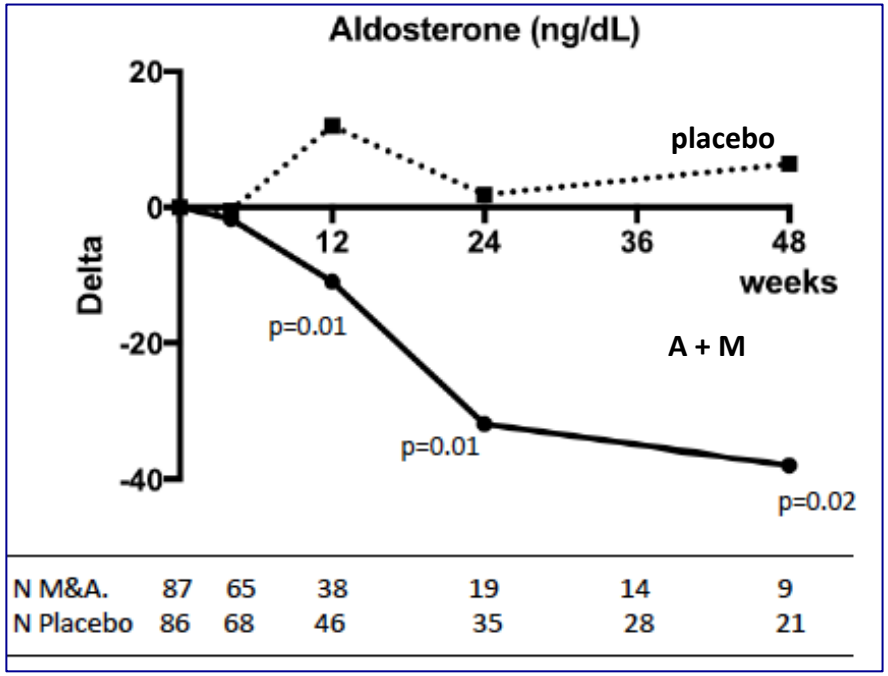


* = times versus compensated cirrhosis

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

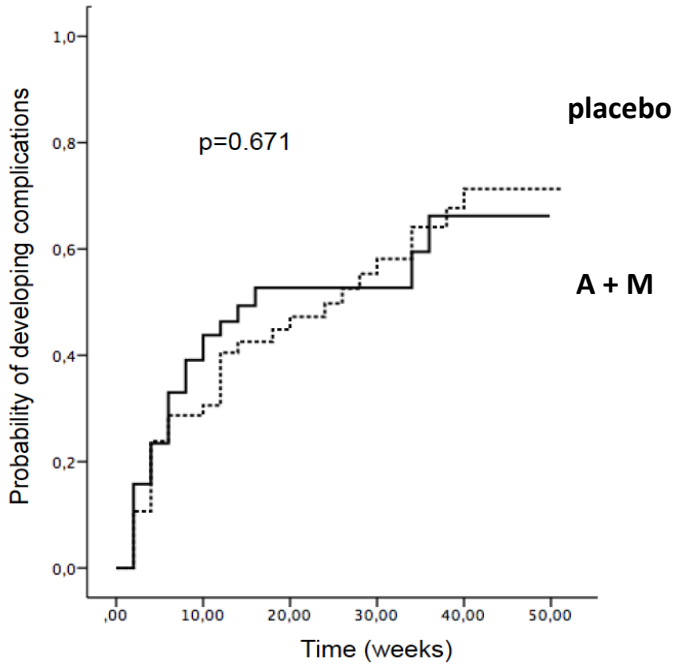




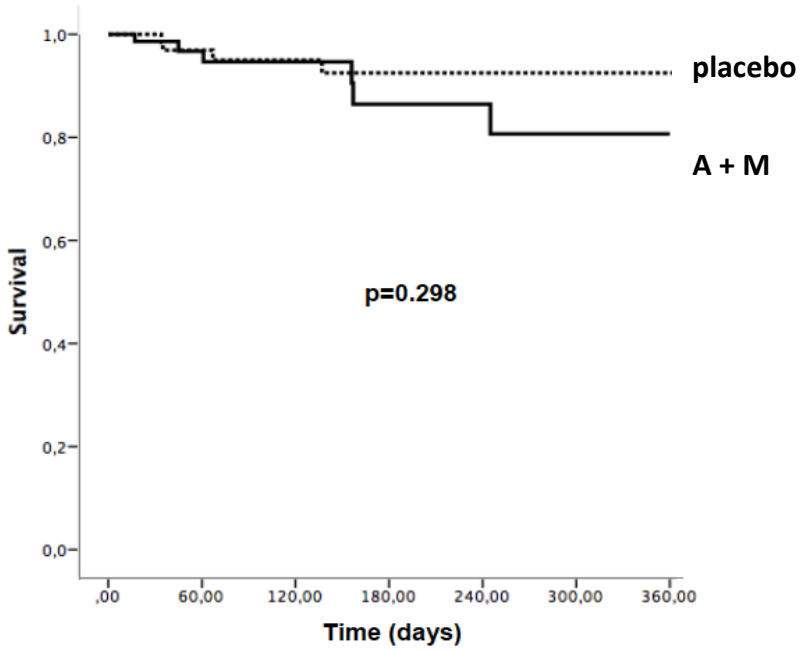
E. Sola et al. J Hepatol. 2018 ; 69 : 1250-1259

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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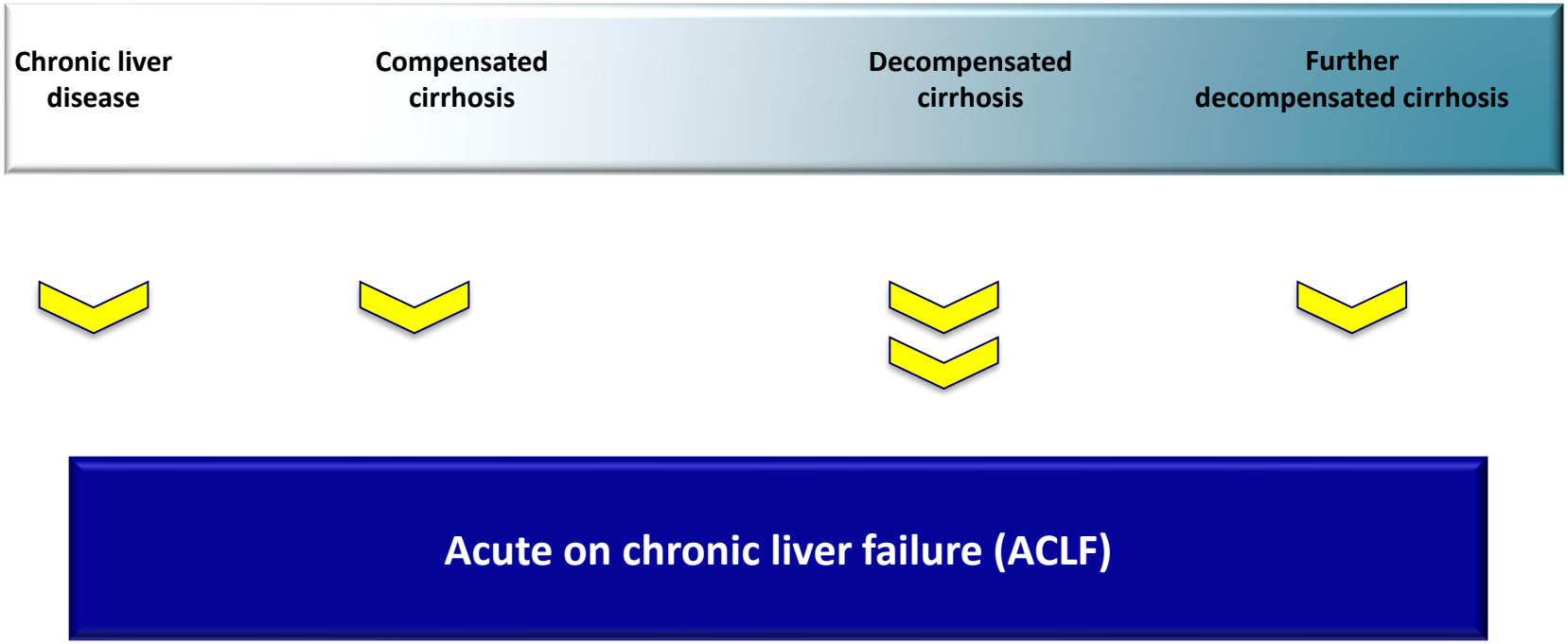
Natural history of cirrhosis



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 %

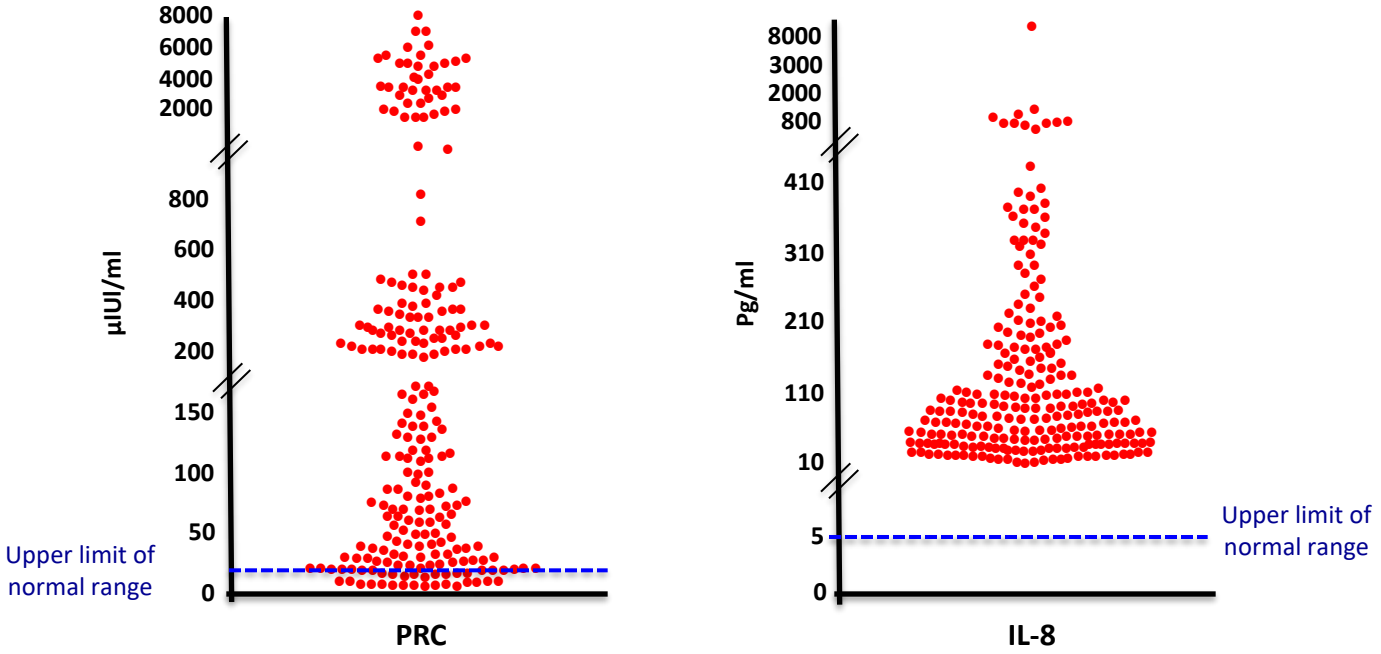
R. Moreau et al. (Canonic study) Gastroenterology 2013 ; 144 : 1426-1437

Main differences in the APALS and EASL-Clif definitions of ACLF

Feature	APALS Definition	EASL-Clif Definition	AASLD Definition
Time between insult and ACLF	4 weeks	Not defined	Not defined
What qualifies as "chronic liver disease"	Chronic liver disease with or without underlying chirrosis	Cirrhosis including decompensated cirrhosis	Cirrhosis including decompensated cirrhosis
Interval in which there is an high mortality	Not defined	28 days and 3 months	3 months
Rate of mortality	Not defined	> 15 % at 28 days	Not defined
What qualifies as precipitants ?			
• Alcohol, drugs, hepatotropic viruses, and surgery	Yes	Yes	Not evaluated
• Bacterial infections	No	Yes	Yes
• Variceal bleeding	Yes	Yes	Not evaluated
Definition of organ failures	Serum bilirubin > 5 mg/dl, INR > 1.5 plus ascites and/or hepatic encephalopathy (HE)	CLIF-SOFA score	Grade III or IV HE MAP < 60 mm Hg Need of mechanical ventilation Need of RRT

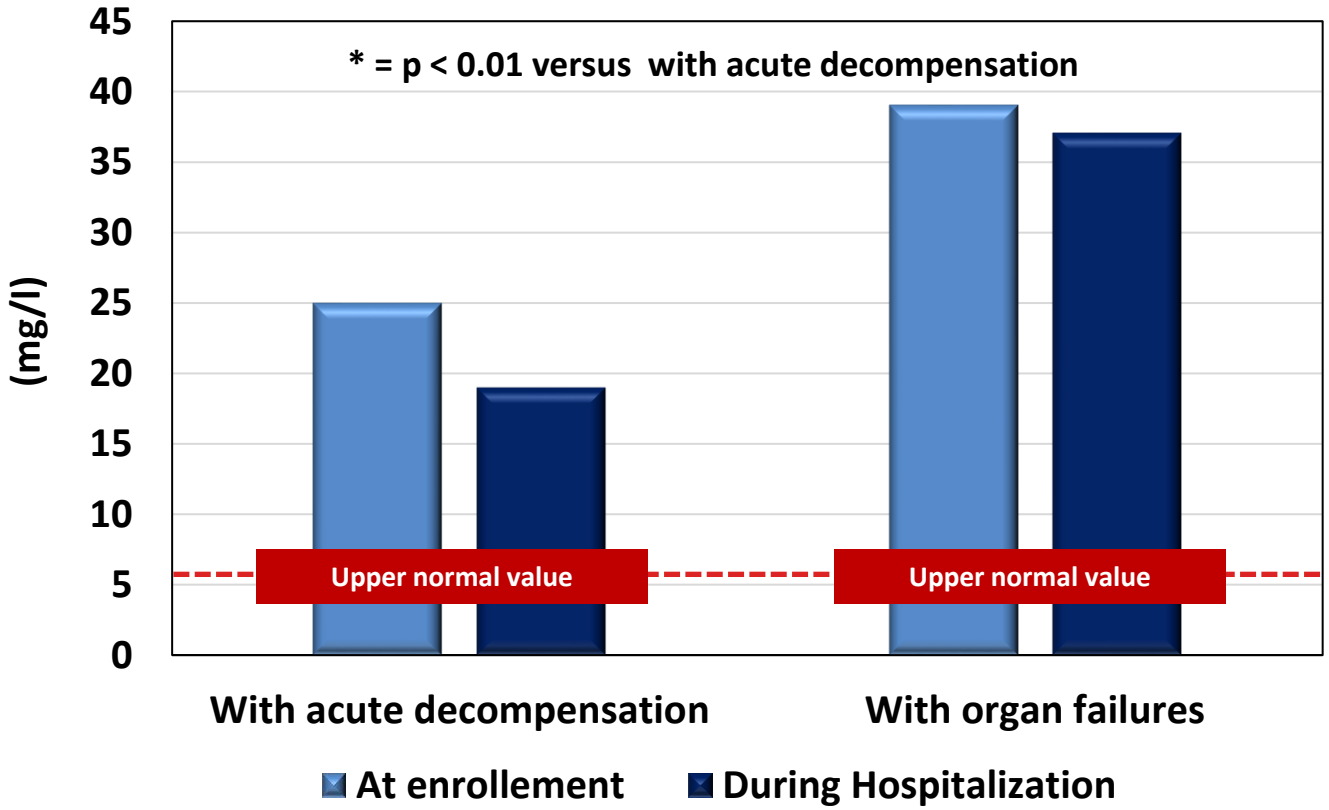
Adapted from JS Bajaj Gastroenterology 2013 ; 144 : 1337-1339

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



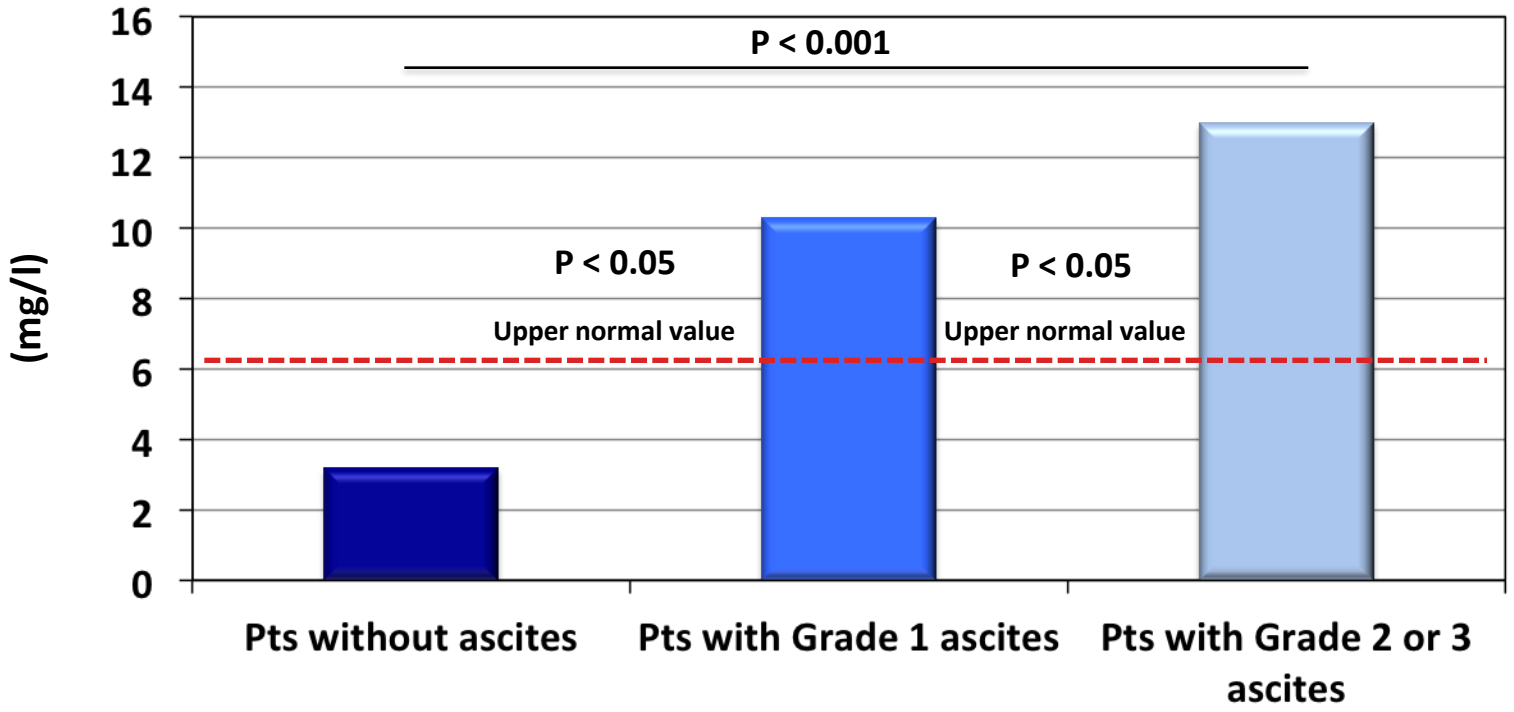
J. Claria et al. Hepatology 2016 ; 64 : 1249-1264

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



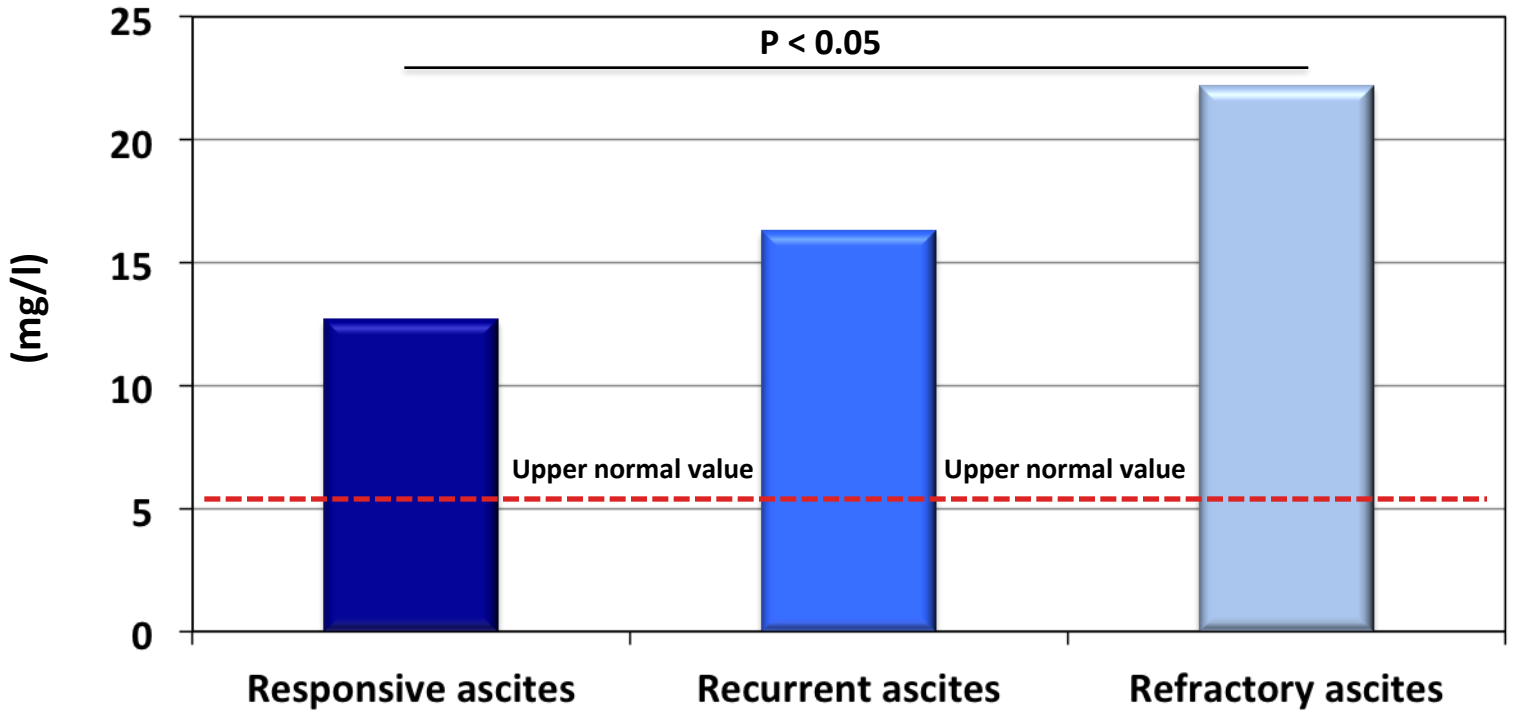
R. Moreau et al. (Canonic study) Gastroenterology 2013 ; 144 : 1426-1437

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



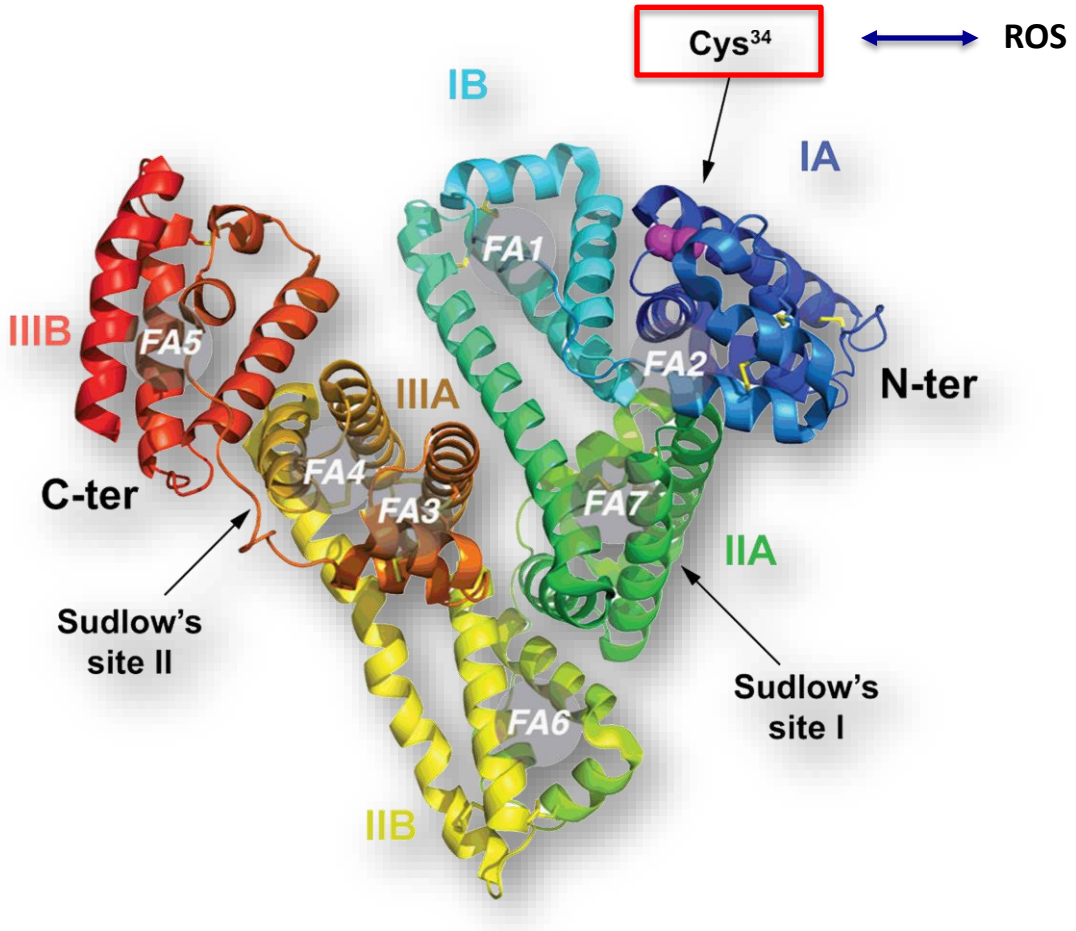
M. Tonon et al. Clin. Gastroenterol. Hepatol. 2021 ; 19 : 358-366

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



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

Albumin molecule with the main binding domains



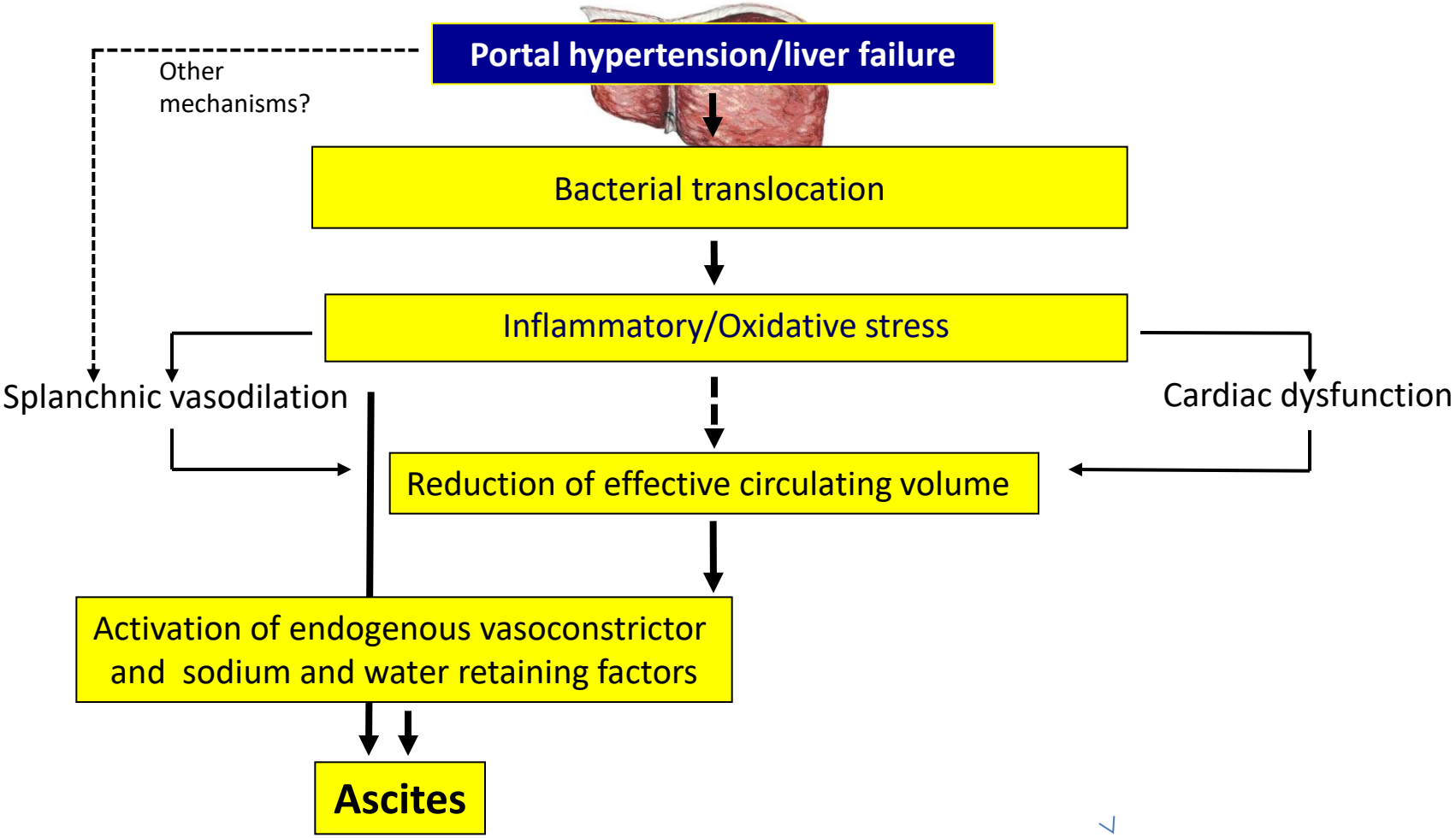
R. Jalan et al. Hepatology 2013 ; 59 : 918-920

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

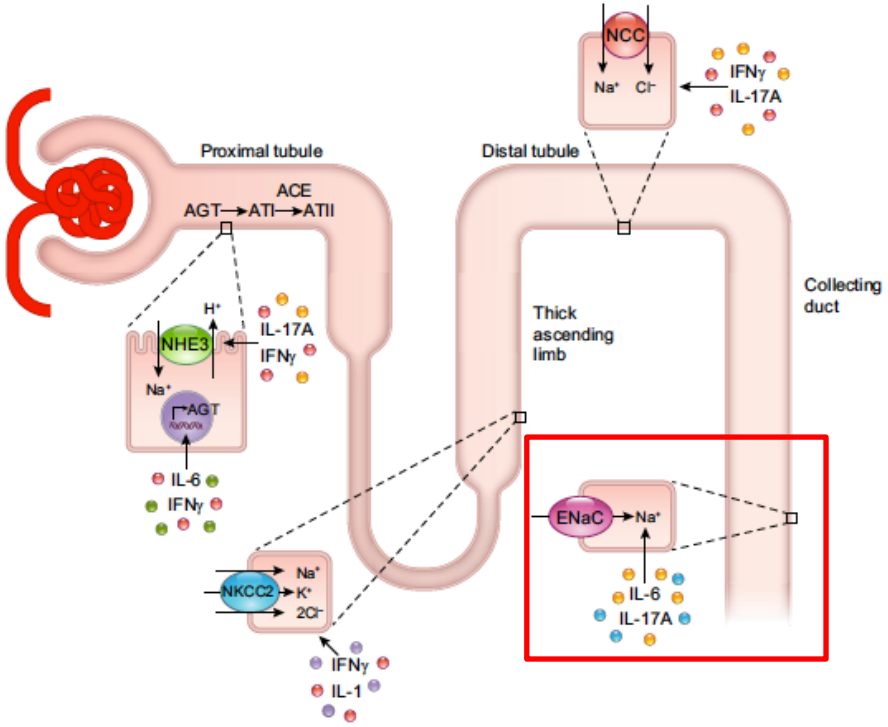
J. Claria et al. Hepatology 2016 ; 64 : 1249-1264

New pathophysiological hypothesis



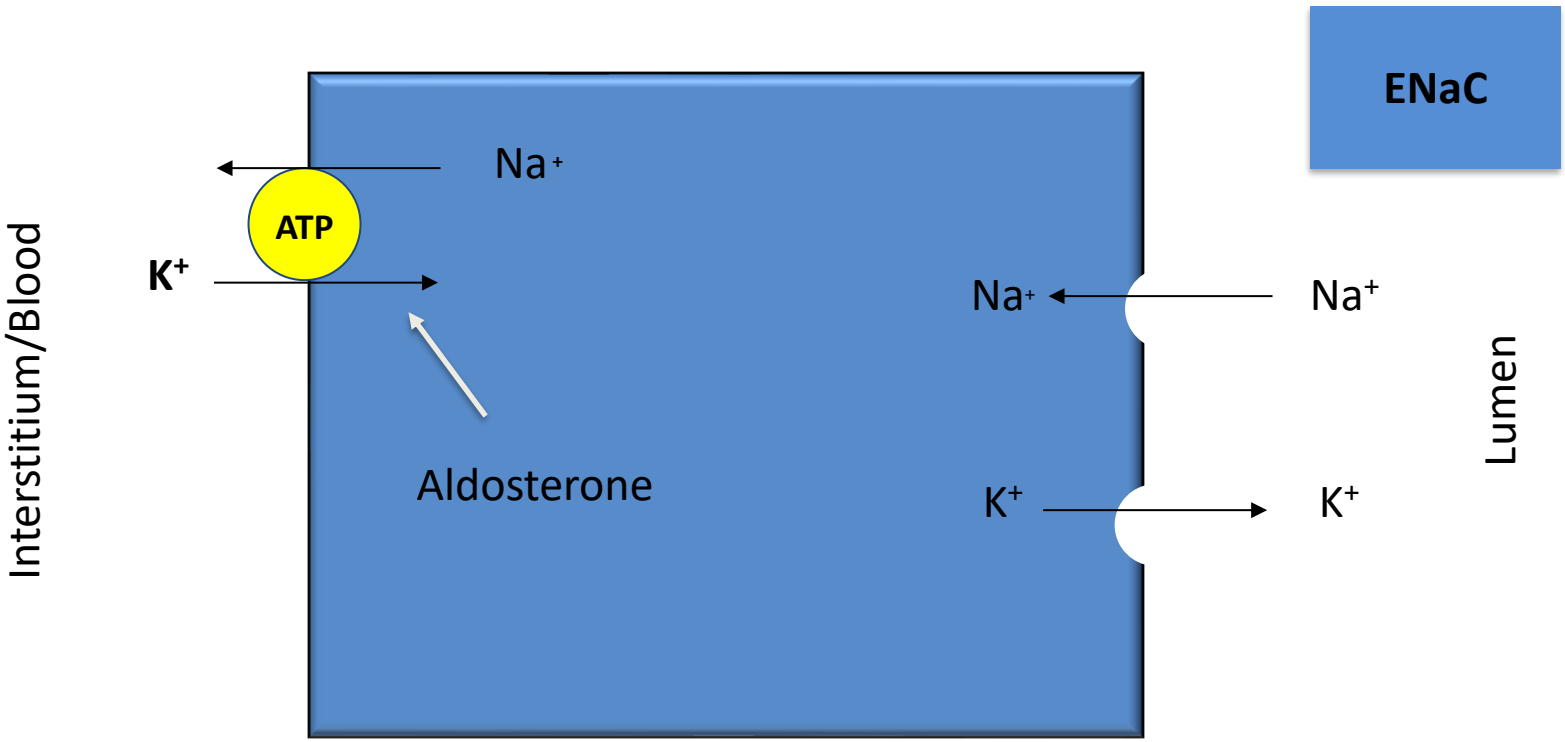
Adapted from M. Bernardi et al. J. Hepatol. 2015 ; 63 : 1272 - 1284

Reanal trasporters activated by inflammatory cytokines

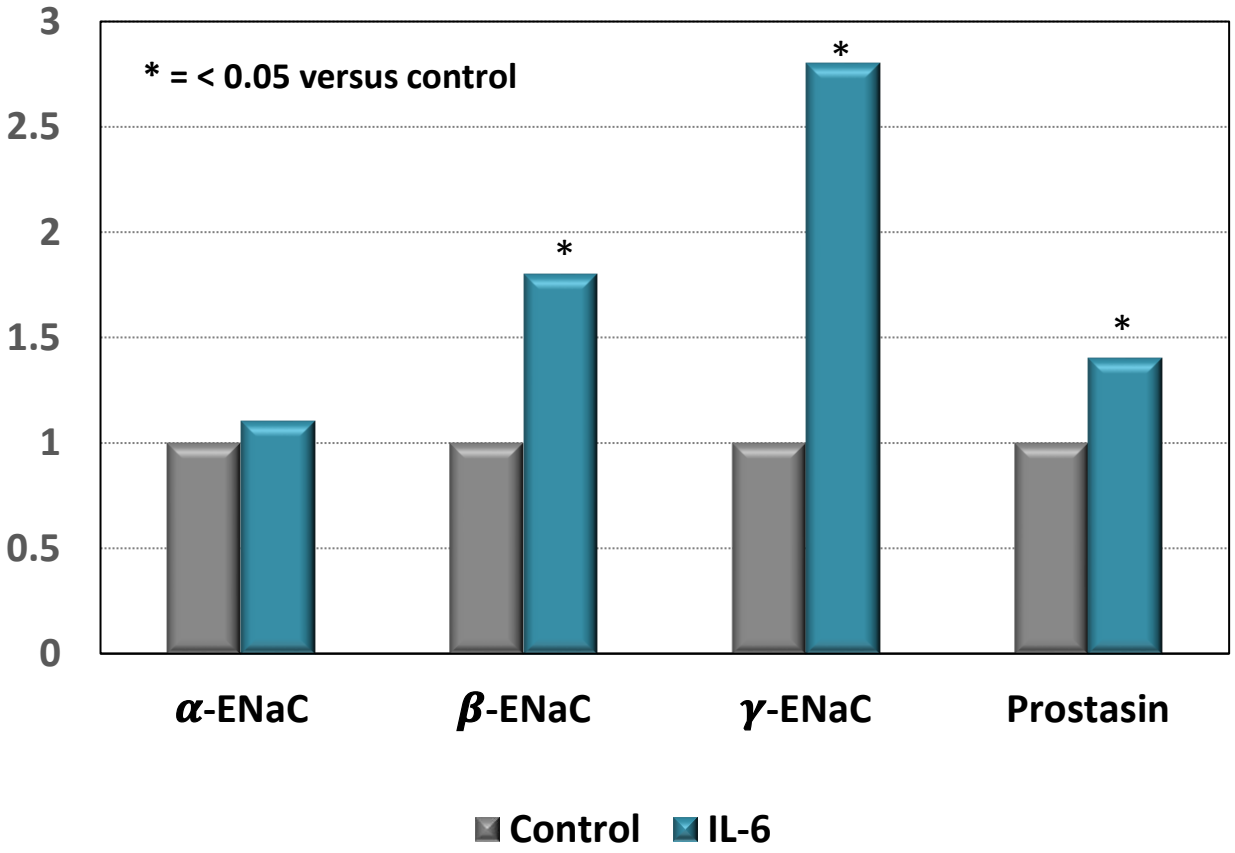


A.E. Norlander et al. Am. J. Renal Physiol. 2017 ; 313 : F141-F144

Mechanisms of sodium reabsorption in the collecting duct

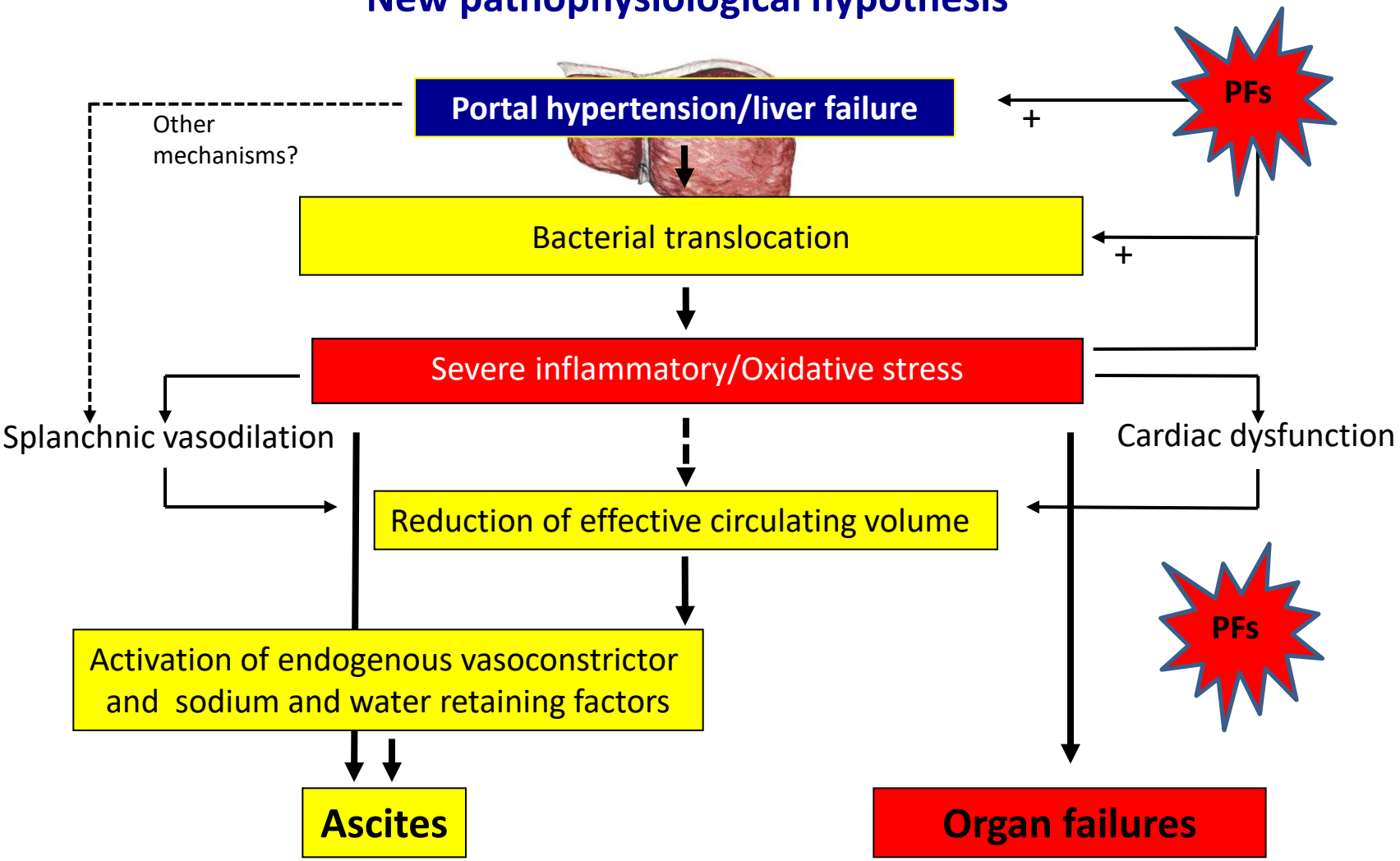


Effects of IL-6 on the gene expression of ENaC subunits and prostasin



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

New pathophysiological hypothesis



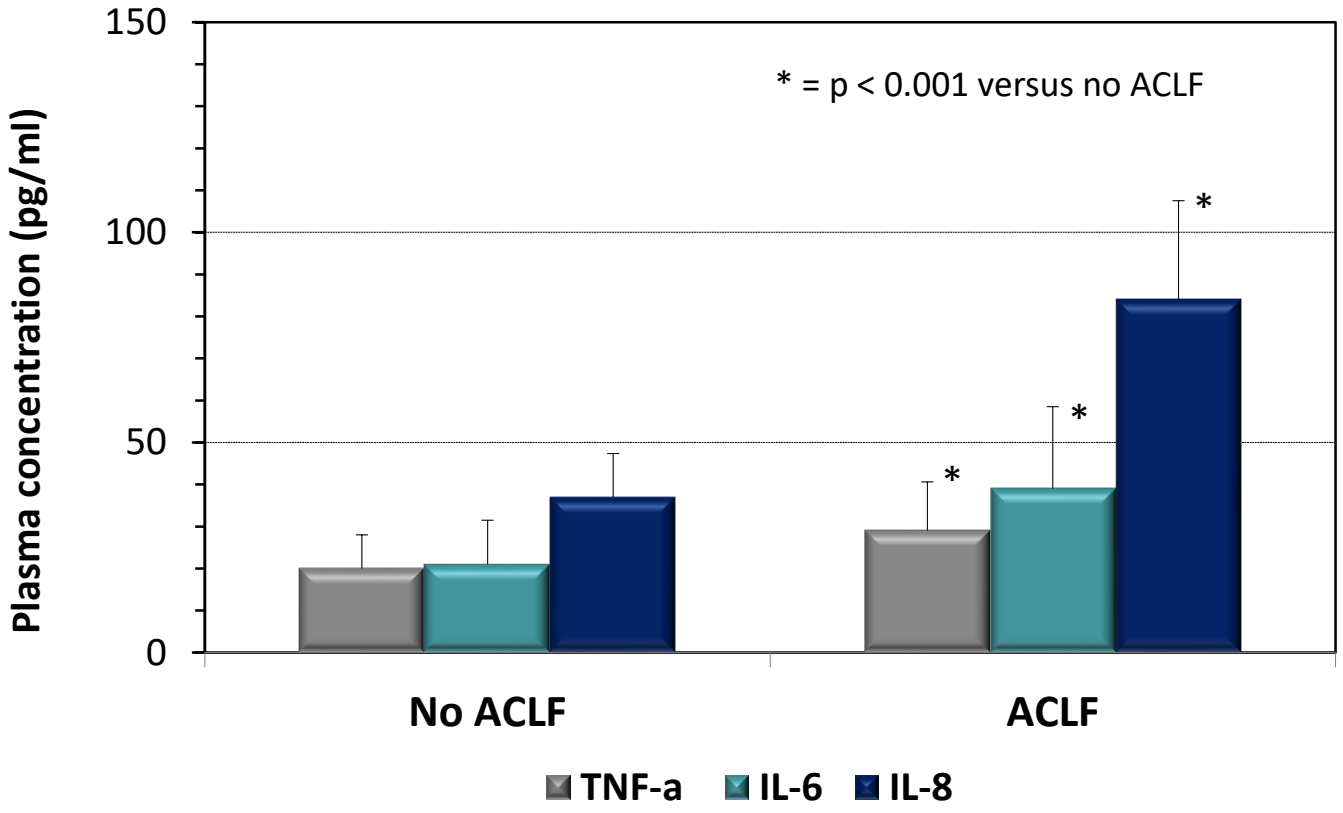
Adapted from M. Bernardi et al. J. Hepatol. 2015 ; 63 : 1272 - 1284

Precipitating factors in patients with AD-ACLF in Europe

Precipitating factor	AD-NO ACLF (n° = 1071)	AD-ACLF (n° = 202)	P
Proven Bacterial infection (%)	29.32	50.0	< 0.001
Alcoholic hepatitis (%)	25.68	43.56	< 0.001
GI bleeding	16.43	19.80	N.S.
Drug induced brain injury (%)	7.84	8.42	N.S.

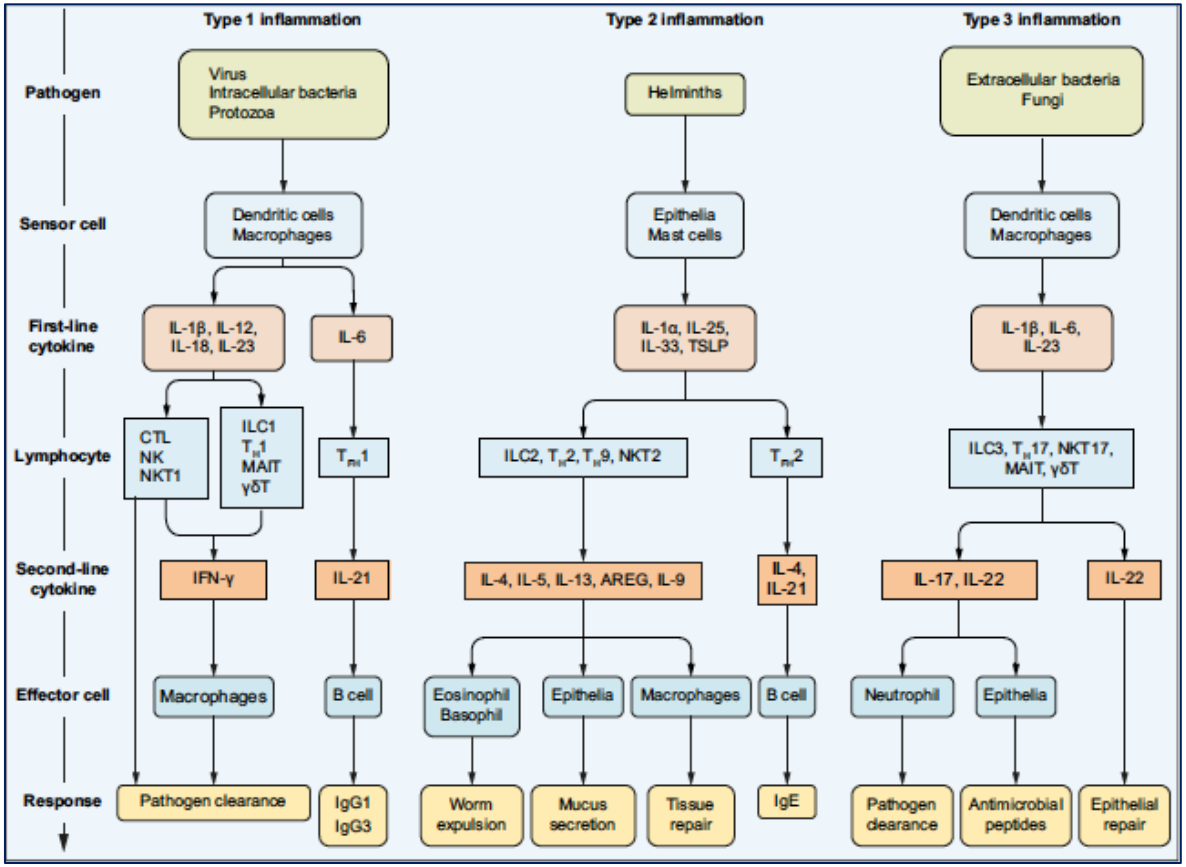
J. Trebicka et al. (Predict study 2) J. Hepatol. 2021 ; 74 : 1097-1108

Plasma cytokines in patients with cirrhosis with or without ACLF



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

Type of inflammatory or immune responses



R. Medzhitov Science 2021 ; 374 : 1070–1075

Phenotypes of inflammation at enrollment

Type of inflammatory response ○ Cytokines	No Organ Dysfunction	Organ Dysfunction no OrganFailure	Organ Failure No ACLF	ACLF	P
Type 1 Inflammatory response					
○ Il-1β (pg/ml)	0.3 (0.1–0.6)	0.4 (0.1–0.8)	0.5 (0.2–0.9)	0.3 (0.1–1.0)	0.053
○ IgG (g/l)	18.4 (14.3–22.1)	19.0 (54.3–23.0)	20.1 (16.3–25.3)	20.1 (15.2–25.3	<0.05
Type 2 inflammatory response					
○ Il-1α (pg/ml)	0.8 (0.3–2.8)	0.9 (0.4–2.0)	1.1 (0.6–2.5)	1.0 (0.4–2.2)	0.492
○ Il-33 (pg/ml)	2.8 (1.4–5.3)	3.2 (1.8–5.8)	5.2 (2.7–8.3)	4.1 (2.5–6.2)	<0.001
○ IL-25 (pg/ml)	1.1 (0.7–2.3)	1.2 (1.7–1.9)	1.9 (1.1–3.6)	2.1 (1.1–3.1)	<0.001
○ Il-13 (pg/ml)	6.8 (3.9-11.7)	7.8 (4.4–12.1)	9.1 (6.2–15.3)	6.7 (2.7–10.4)	<0.025
○ Il-4 (pg/ml)	0.05 (0.02–0.11)	0.07 (0.03–0.0)	0.09 (0.04–0.15	0.09 (0.05–0.16	<0.001
○ Il-21 (pg/ml)	6.8 (3.6–13.8)	7.1 (4.1–12.0)	104 (30.6–310)	125 (52.4–290)	<0.001
Type 3 inflammatory response					
○ IL-6 (pg/ml)	3.7 (2.2–6.39)	4.4 (2.9–6.2)	6.1 (3.5–10.7)	9.3 (5.7–18.5)	<0.001
○ Il-23 (pg/ml)	5.4 (2.8-9.7)	5.4 (2.8-7.9)	8.6 (5.1-15.7)	9.3 (5.9-14.0)	<0.001
○ Il-22 (pg/ml)	1.1 (0.6–2.2)	1.2 (0.7-2.2)	1.8 (1.1–3.5)	2.2 (1.2-3.8)	<0.001

Z. Cao et al. J. Hepatol. 2025. ; 82 : 836–850

Phenotypes of inflammation at enrollment

Other Cytokines or markers of inflammation	No Organ Dysfunction	Organ Dysfunction no OrganFailure	Organ Failure No ACLF	ACLF	P
Tumor necrosis factor-a, pg/ml	6.8 (4.1–9.3)	6.5 (4.4–9.5)	8.6 (5.9–13.9)	9.0 (6.2-11.9)	<0.001
Interferon-inducible protein-10, pg/ml	450 (280-890)	450 (284-749	736 (492—1,326)	577 (306–930)	<0.001
Interleukin-8, pg/ml	28.4 (12.9–84.1)	44.3 (17.1–136.2)	113.0 (61.4–225.2	79.0 (32.4–202.4)	<0.001
Monocyte chemotactic protein-1, pg/ml	196 (155-282)	196 (145-304)	287 (215–363)	240 (187–331)	<0.001
Macrophage inflammatory protein-1b, pg/ml	129 (89.9–192)	133.3 (97.5–198)	211 (141–345)	218 (123–324)	<0.001
Macrophage inflammatory protein-3a, pg/ml	41.3 (25.4–82.7)	58.5 (31.2–94.2)	139 (79.7–269)	112 (81.6–168)	<0.001
Interleukin-10, pg/ml	0.6 (0.3–1.0)	0.7 (0.3-1.2)	1.4 (0.7–2.9)	1.8 (0.9–3.5)	<0.001
Soluble CD163, ng/ml	1,543 (1,091–2,803)	2,383 (1,126–3,719)	4,351 (3,373- –6,800)	5,557 (3,607—7,658)	<0.001
Granulocyte colony-stimulating factor, pg/ml	11.4 (8.6-17.5)	11.0 (7.6-16.3)	10.4 (7.2-16.5)	10.1 (6.8-15.6)	N.S.

Z. Cao et al. J. Hepatol. 2025. ; 82 : 836–850

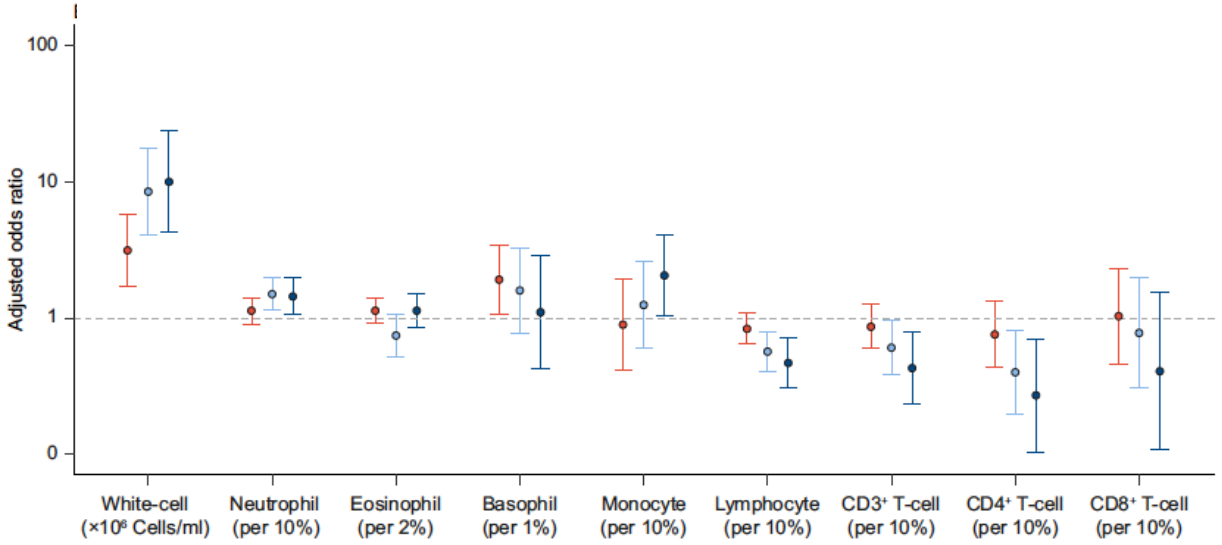
Inflammation in patients with and without ACLF

	Healthy Subjects	AD	ACLF	ACLF due to bacterial infections	ACLF due to active alcohol abuse
TNFα	9 (7-12)	20 (14-27)	29 (17-41	32 (26-47)	21 (14-32)
IL-6	0.3 (0.3-0.3)	21 (11-41)	39 (7-115)	72 (28-358)	37 (13-122)
IL-8	1.6 (1.6-3.3)	37 (20-76)	84 (41-169)	92 (47-167)	211 (141.351)

$P < 0.001$

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

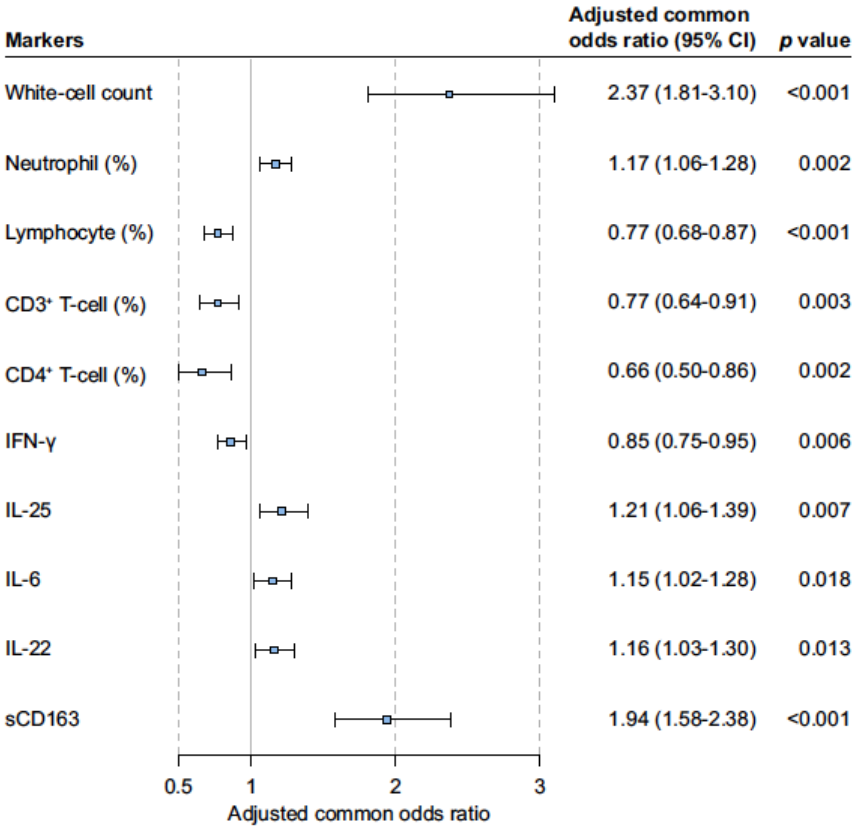
Blood immune cell counts from acutely decompensated cirrhosis to ACLF



● Organ Dysfunction ; ● Organ Failure without ACLF ; ● Organ Failure with ACLF

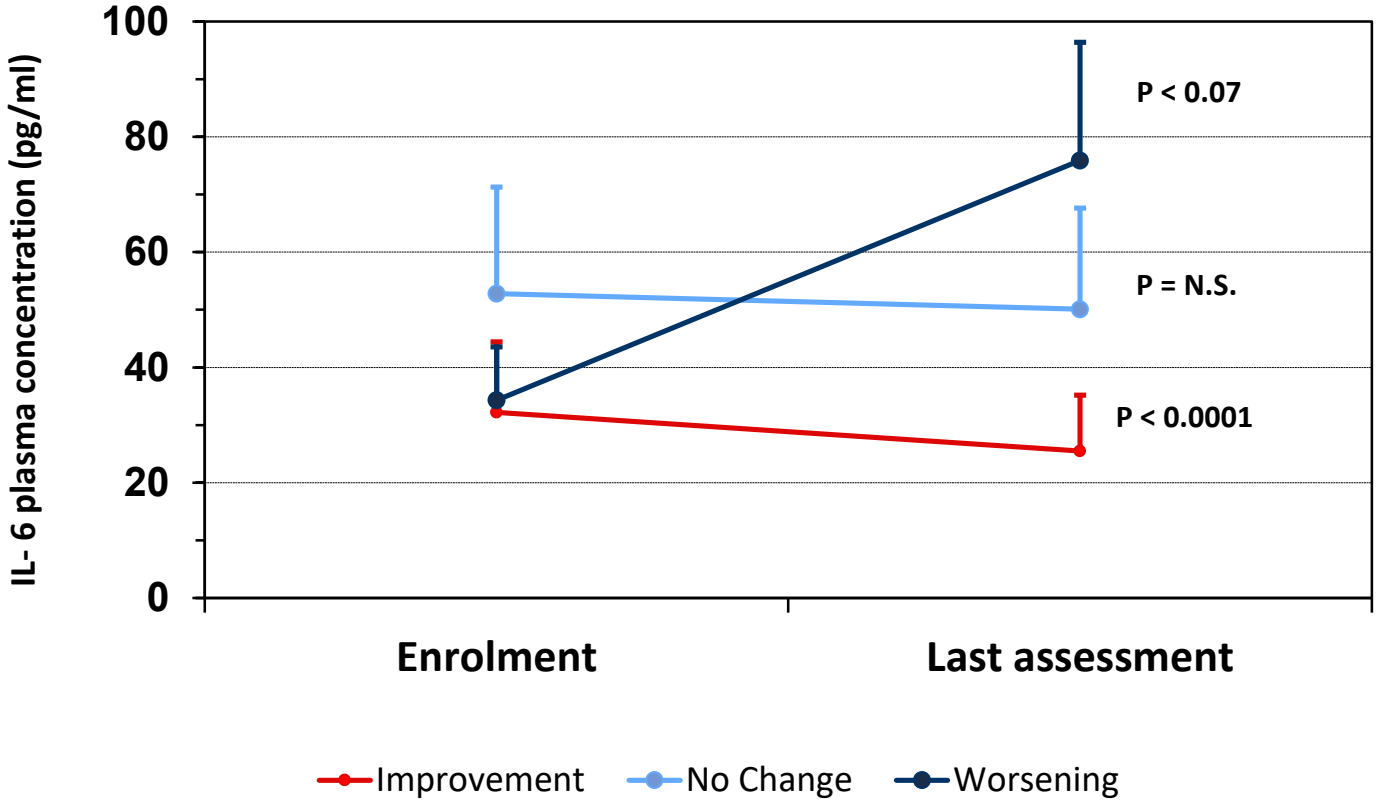
Z. Cao et al. J. Hepatol. 2025. ; 82 : 836–850

Markers of inflammatory response associated with from acutely decompensated cirrhosis to ACLF



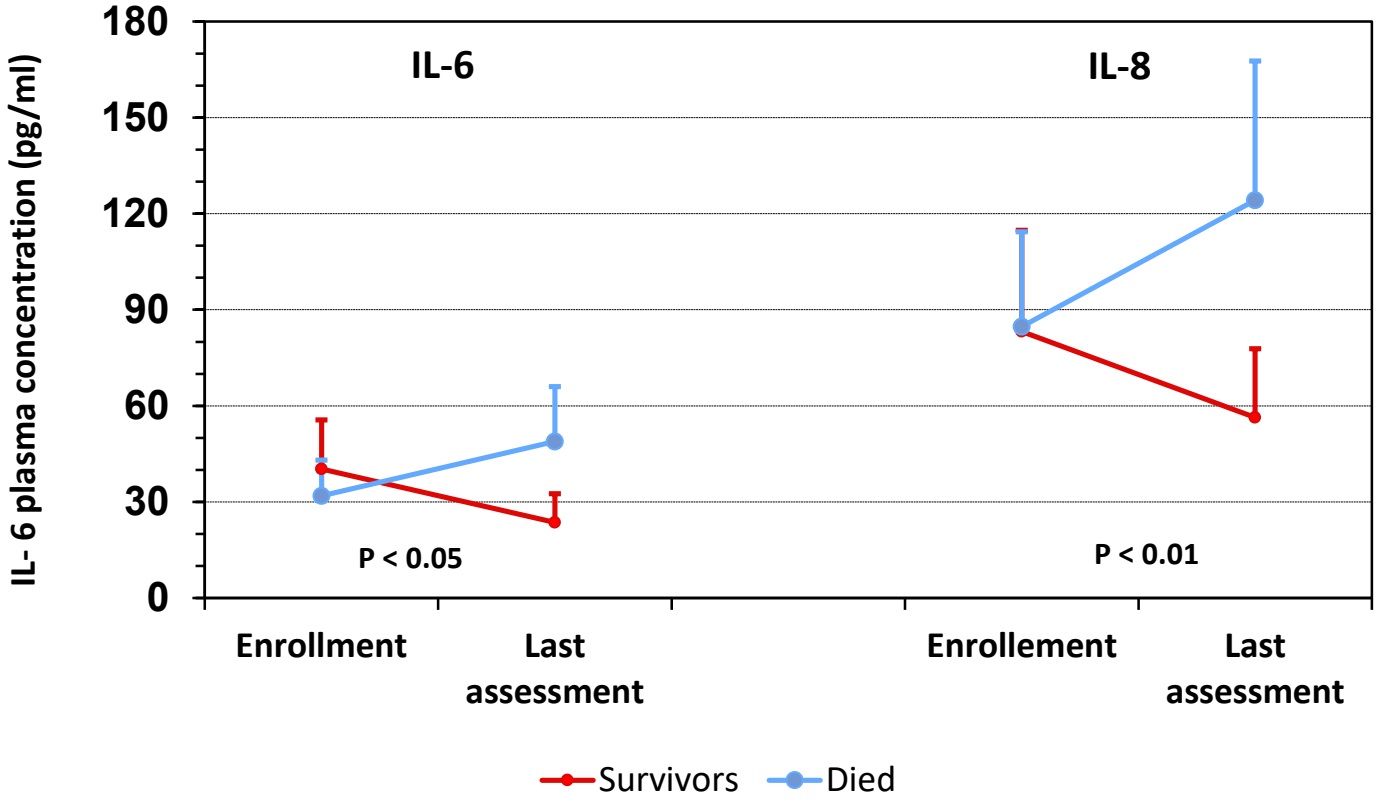
Z. Cao et al. J. Hepatol. 2025. ; 82 : 836–850

Plasma cytokines in patients according to the clinical evolution of ACLF



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

Plasma cytokines in patients according to the 90 day survival or death



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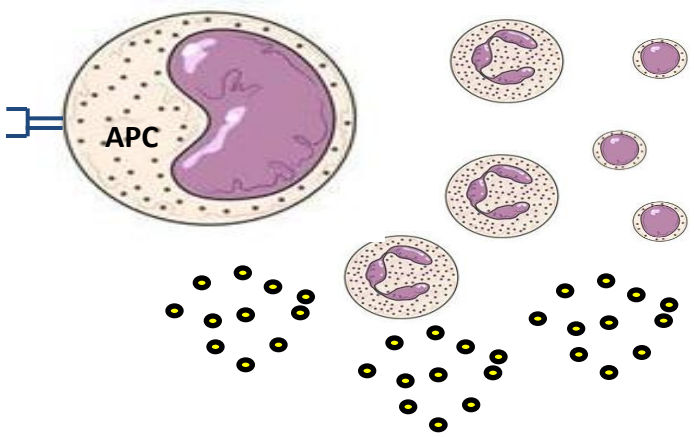
Patogenesis of organ failure/s

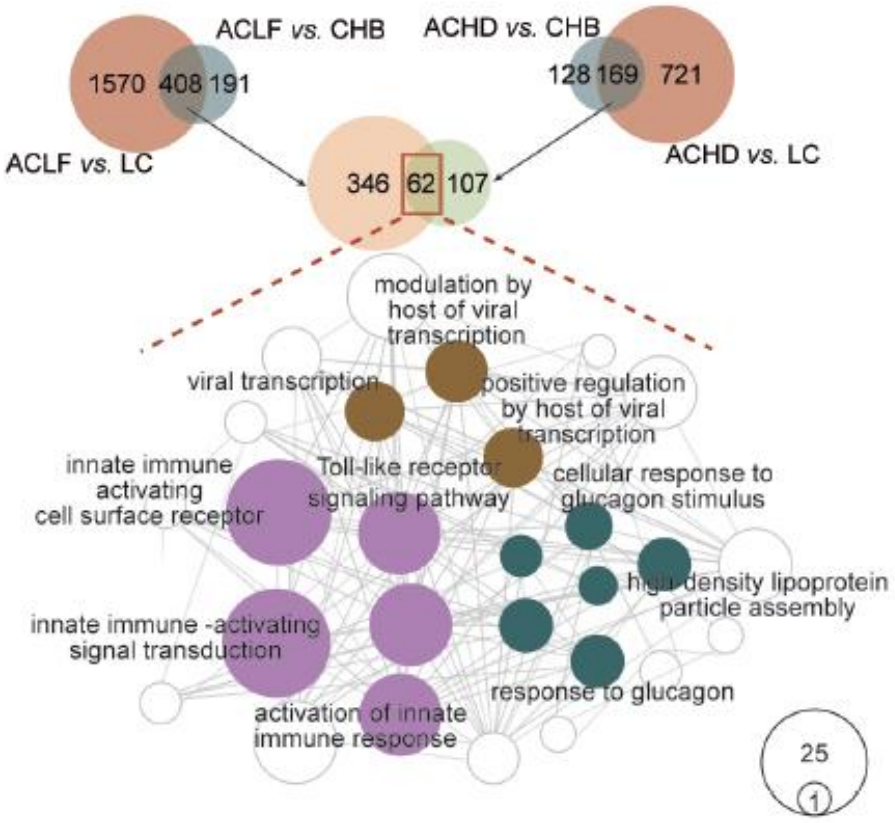
PAMPS or DAMPS



Immune Dysfunction and ACLF

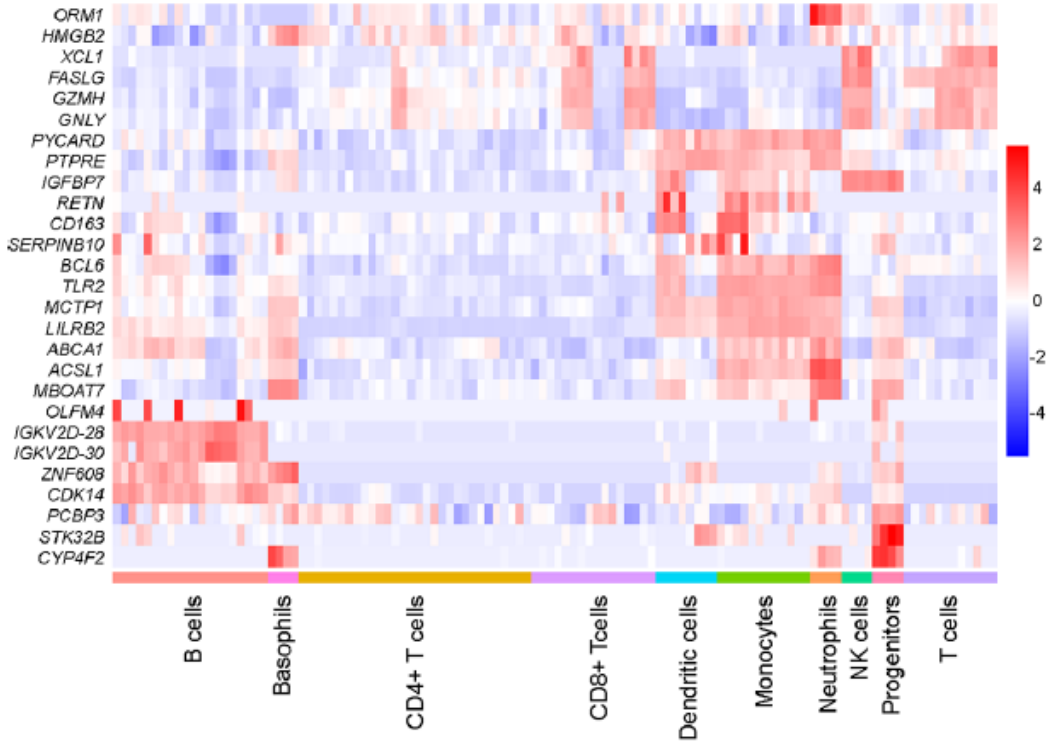
- High grade systemic inflammation
- Upregulation of innate immune response

Network of the biological processes identified in a functional synergy analysis of 62 overlapping significant differentially expressed genes in PBMCs



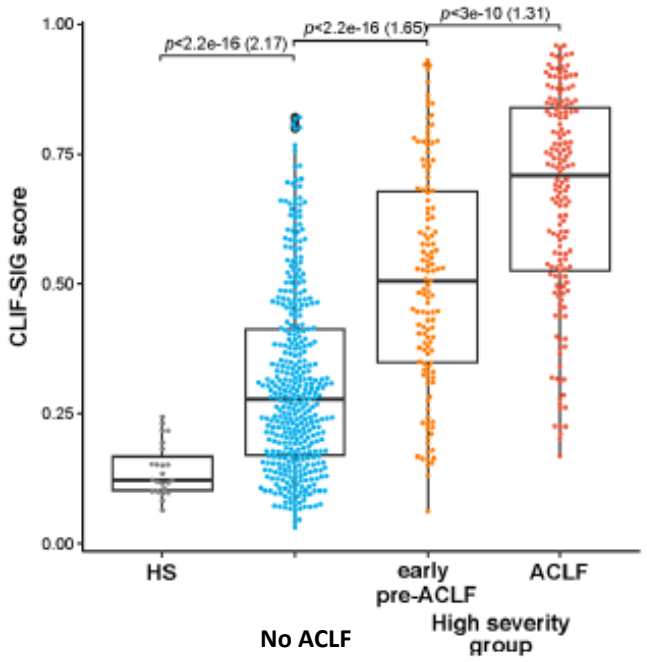
Li J. et al. Gut 2022 ; 71 : 163–175

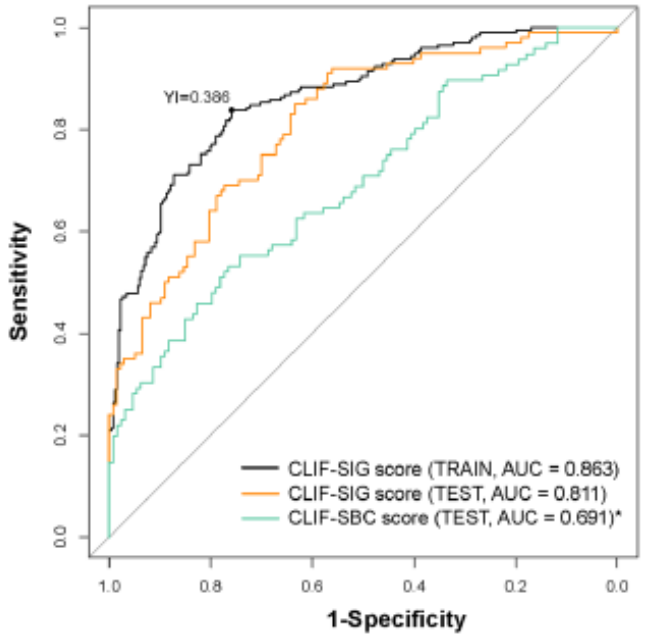
Genes diferentially expressed by immune cells in patients with AD with or without ACLF



J. Trebicka et al. Gut ; 2025 : 696-716

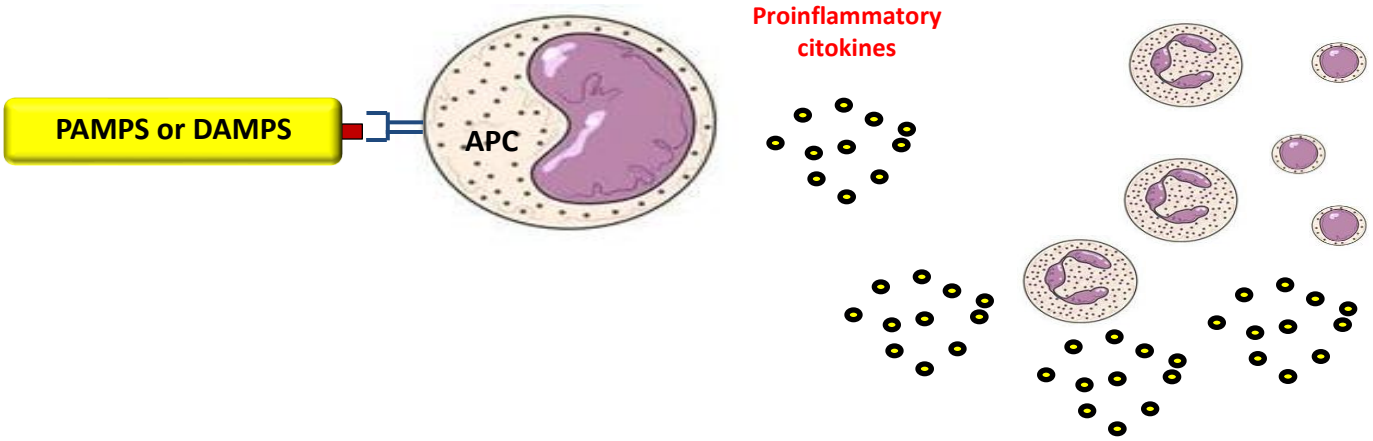
Prediction of development of ACLF in patients with cirrhosis and AD: a gene score (SIG score) versus a standard biomarkers composite score (SBC score)



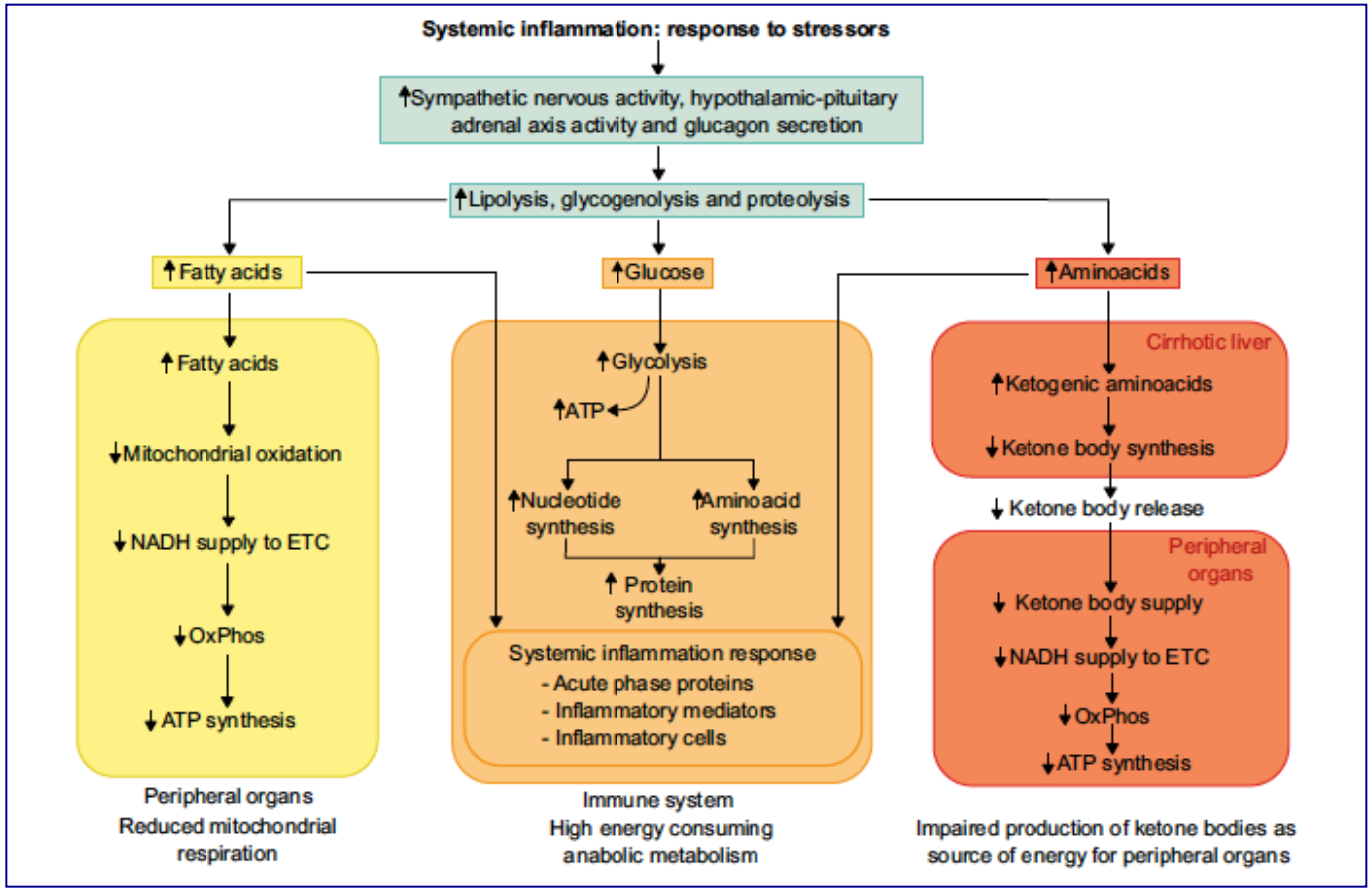


J. Trebicka et al. Gut ; 2025 : 696-716

Patogenesis of organ failure/s

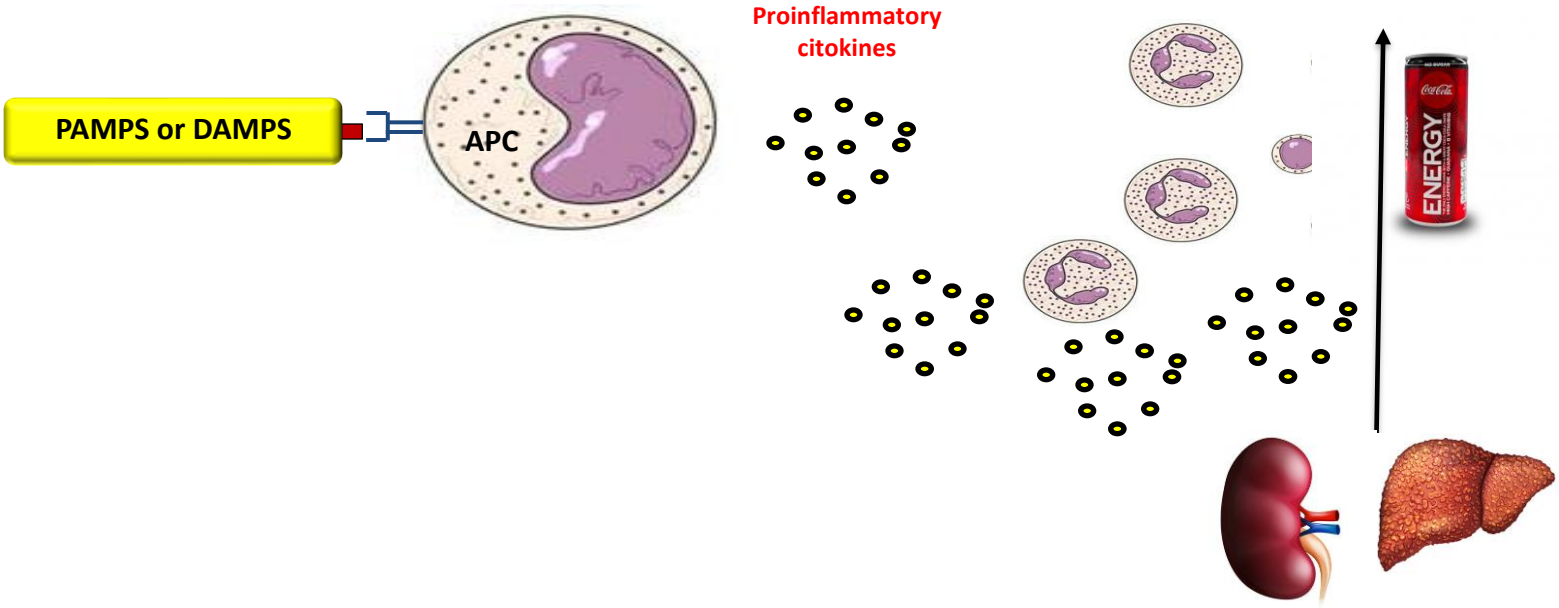


Impaired function and damage of mitochondria in patients with AD

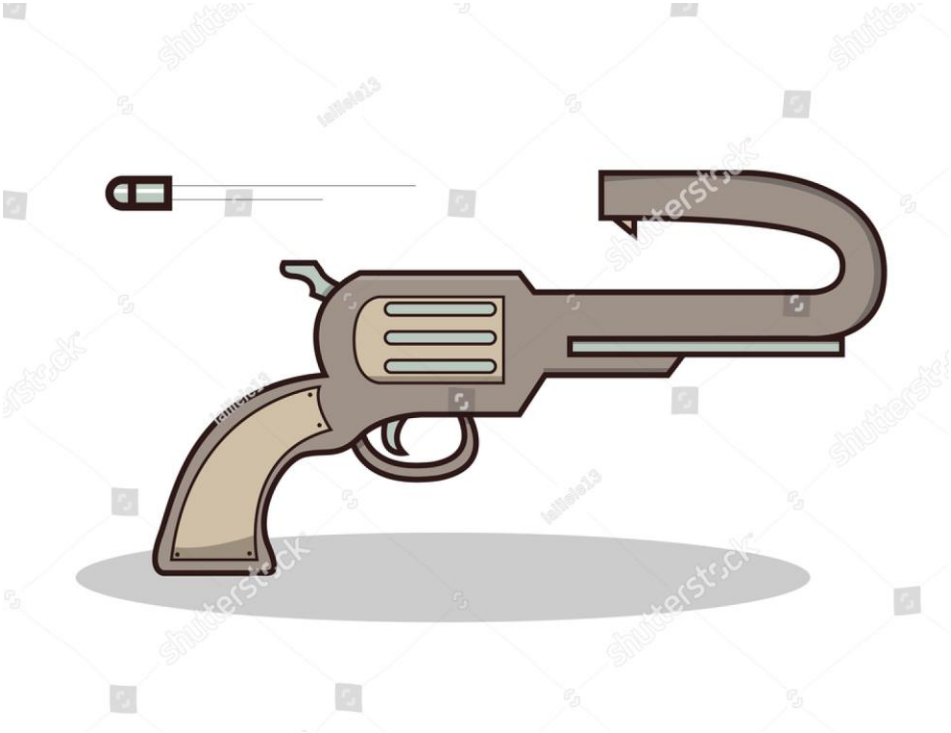


V. Arroyo et al. J. Hepatol. 2021 ; 74 : 670-685

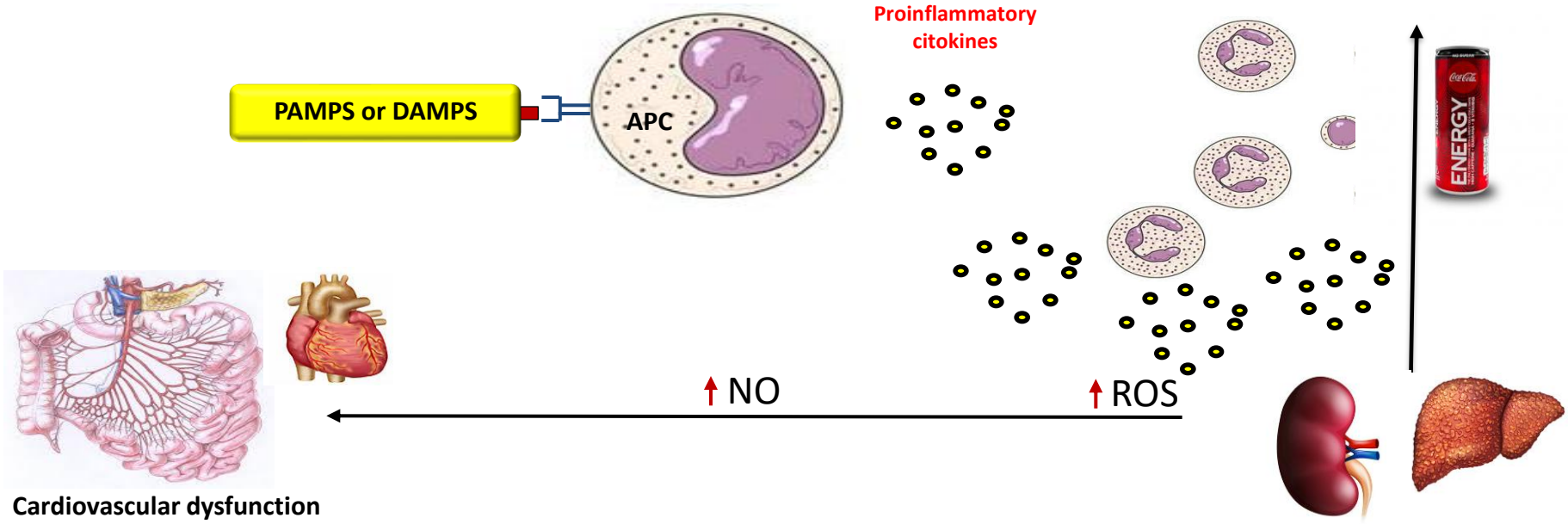
Patogenesis of organ failure/s



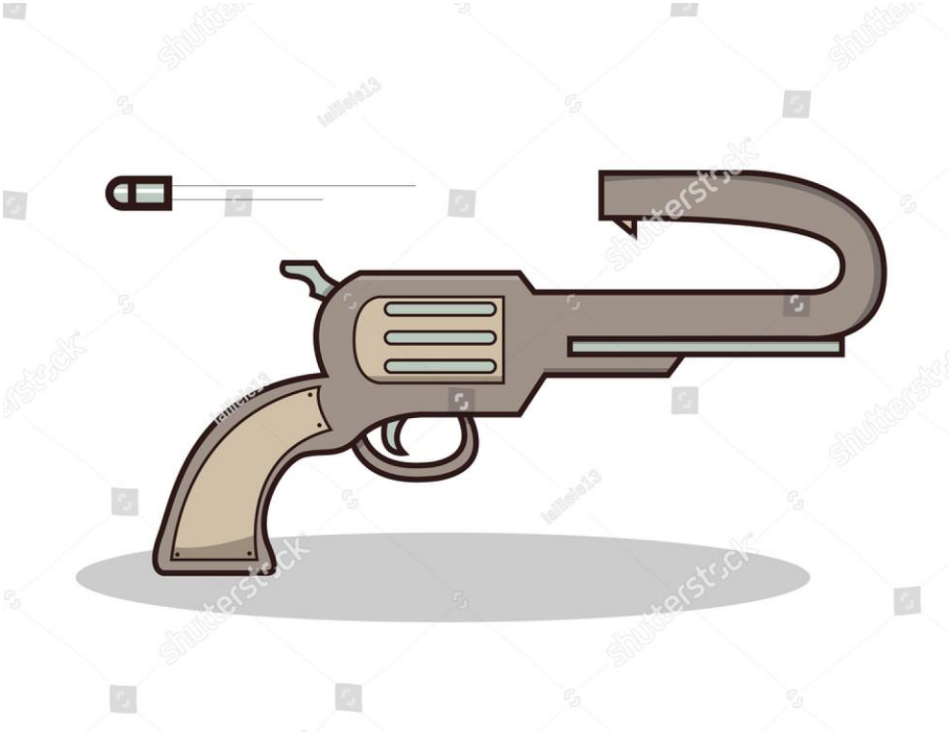
Friendly fire



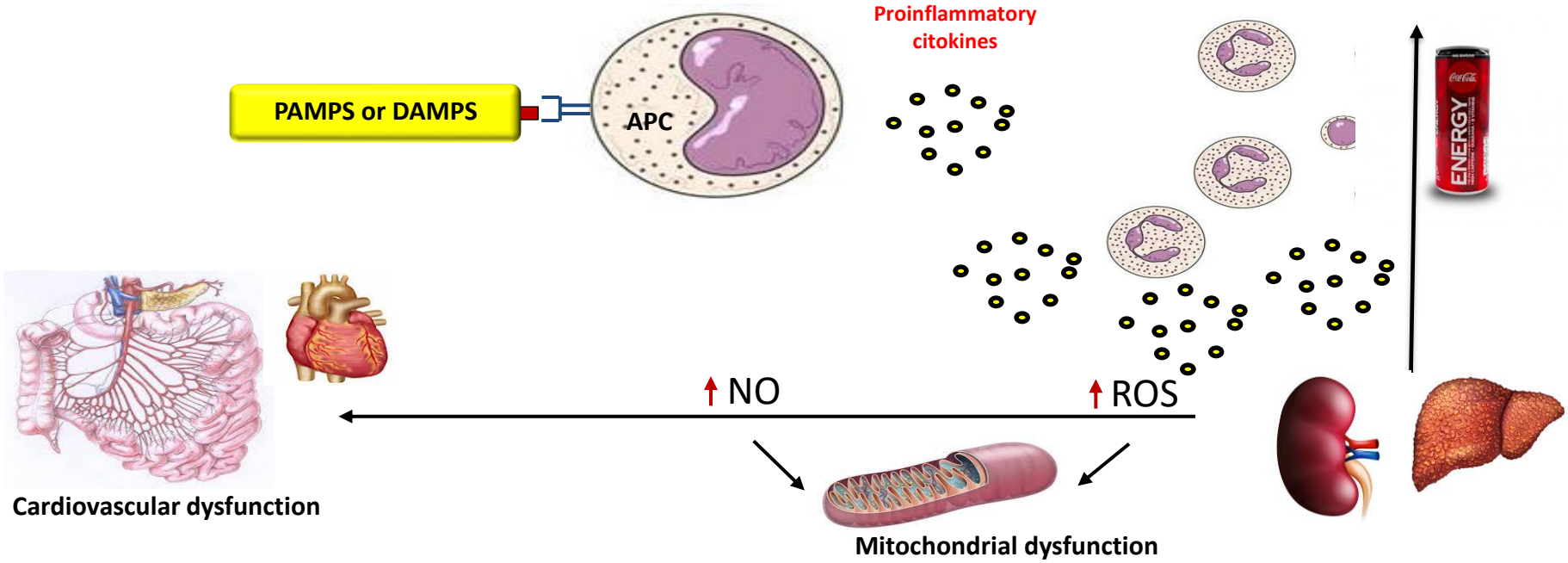
Patogenesis of organ failure/s



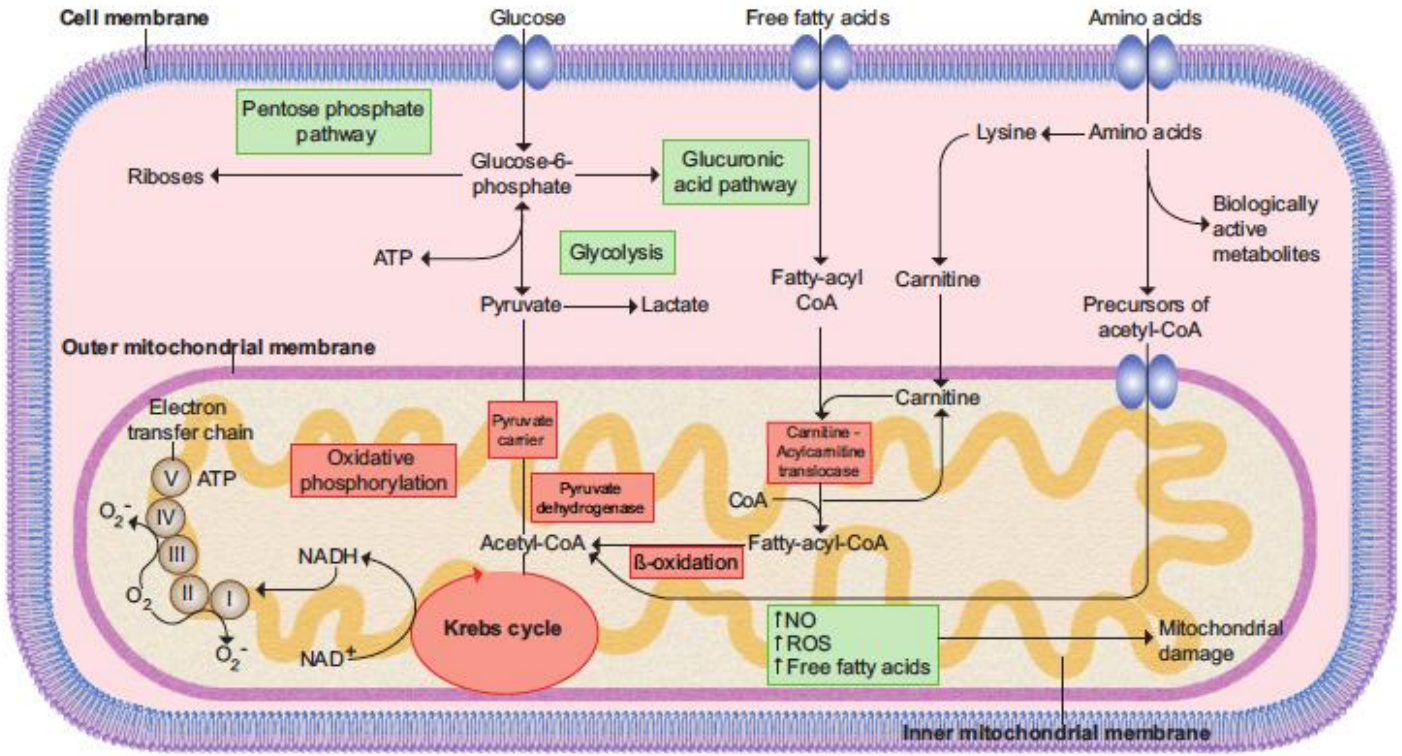
Friendly fire



Patogenesis of organ failure/s

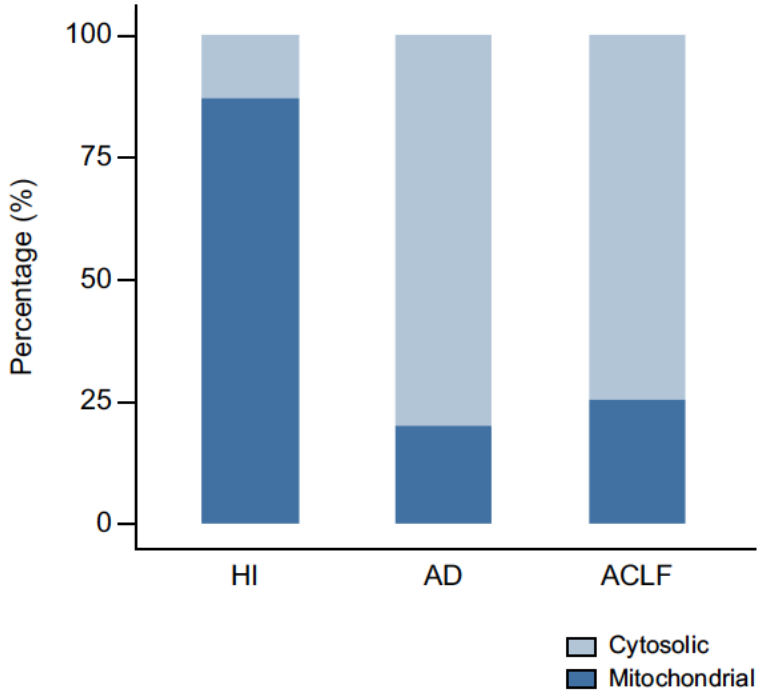


Impaired function of mitochondria and mitochondria damage in patients with AD



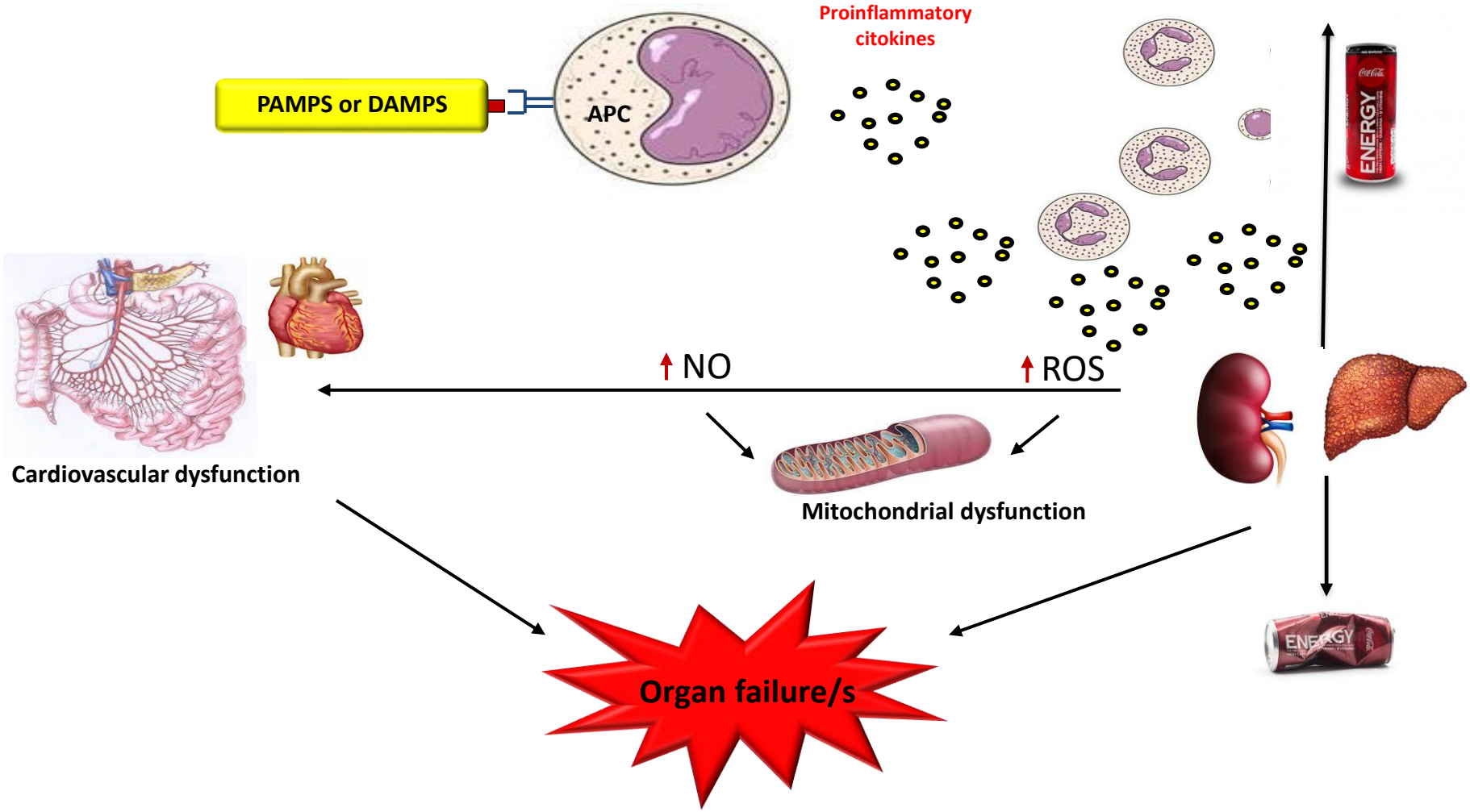
V. Arroyo et al. J. Hepatol. 2021 ; 74 : 670-685

Percentage share of the sum of signals of mitochondrial energy production compared to the sum of signals from the whole cell energy output

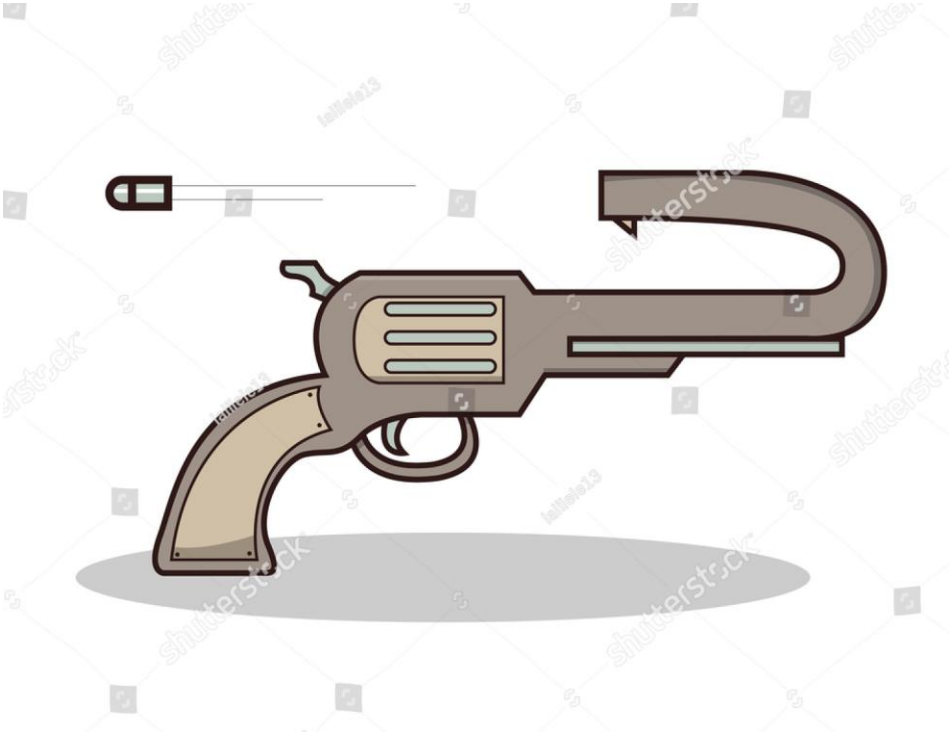


I.W. Zhang et al. J. Hepatol. 2022, 76, 93–106

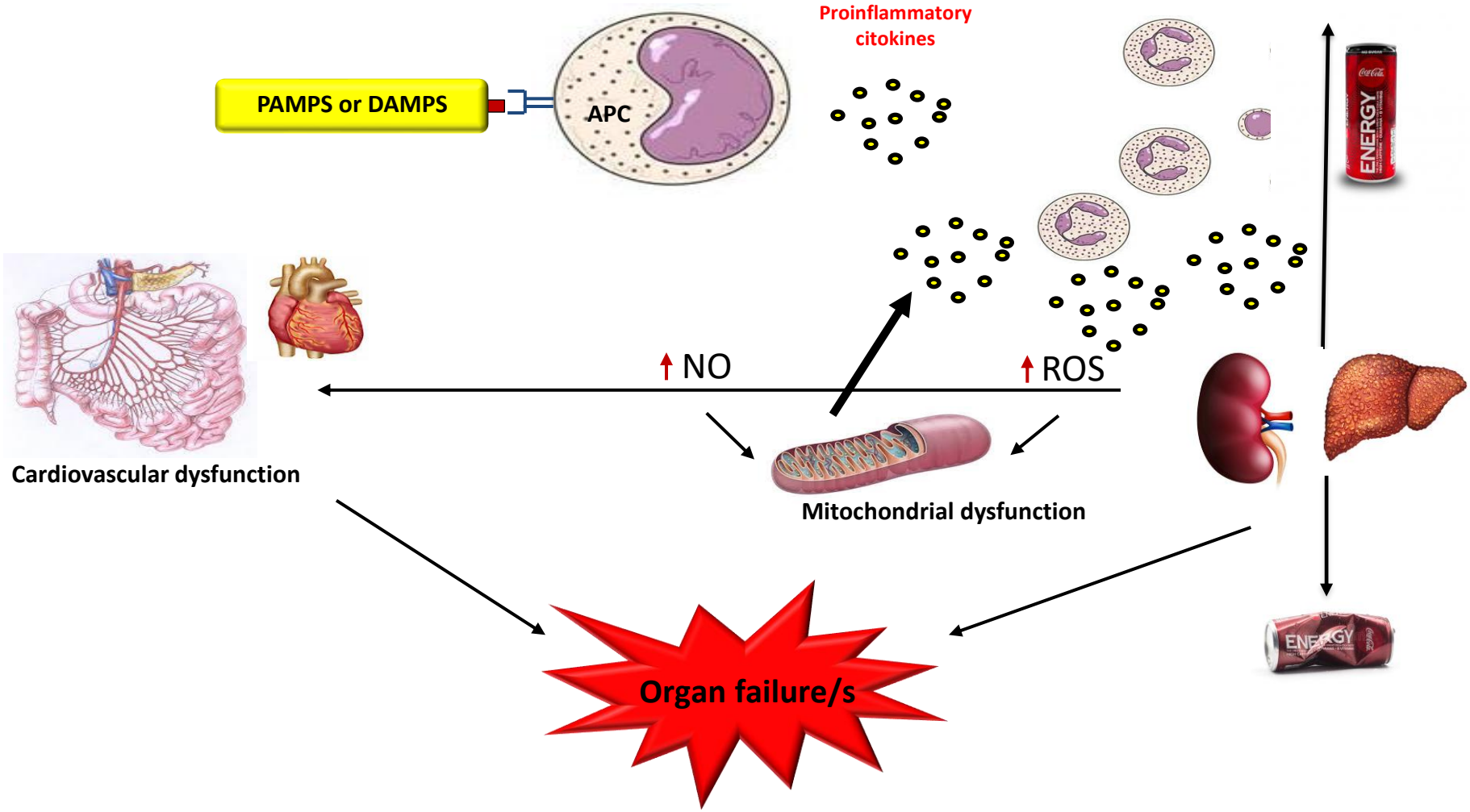
Patogenesis of organ failure/s



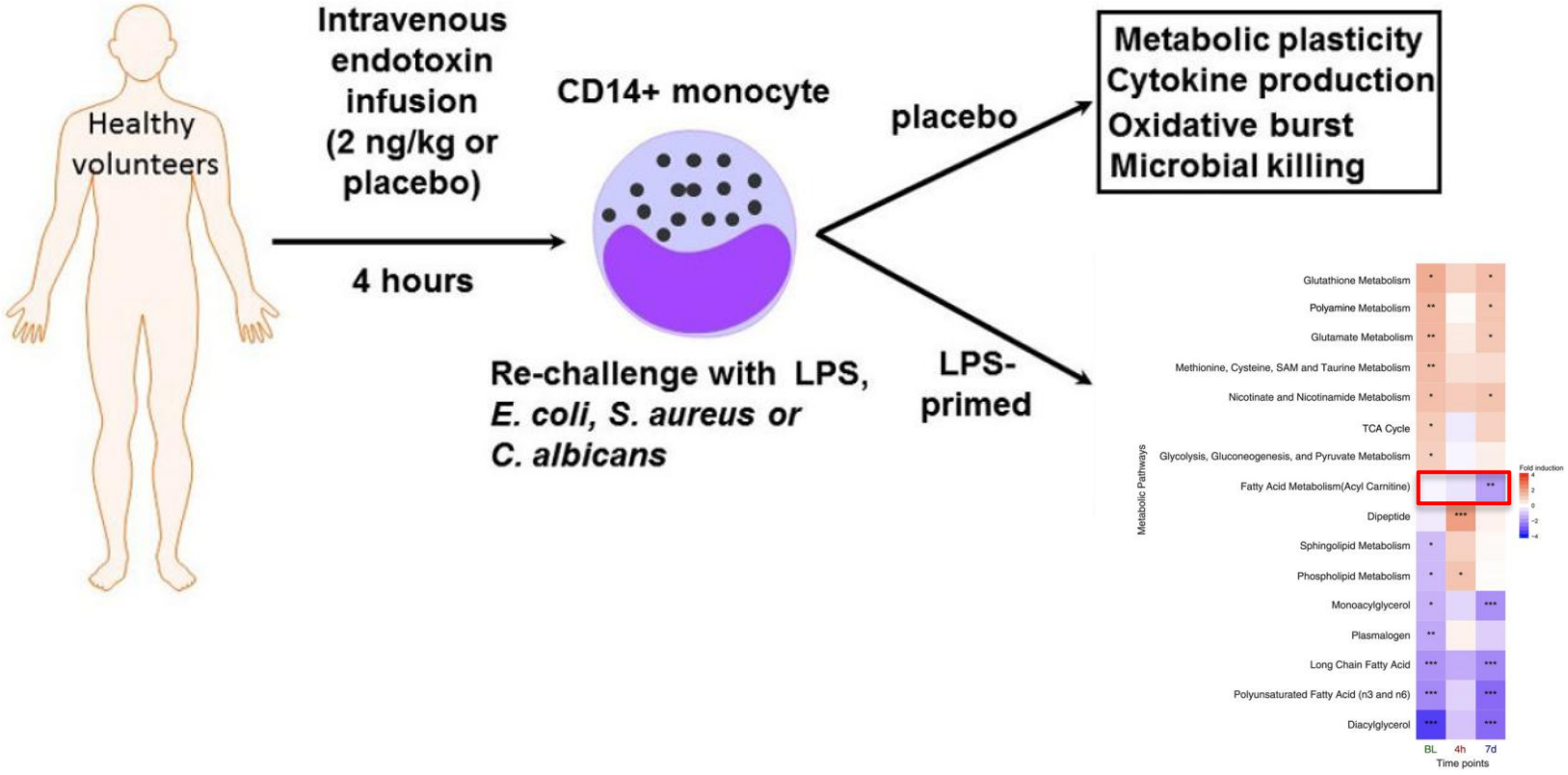
Friendly fire



Patogenesis of organ failure/s



Loss of metabolic plasticity and atimicrobial function in monocytes

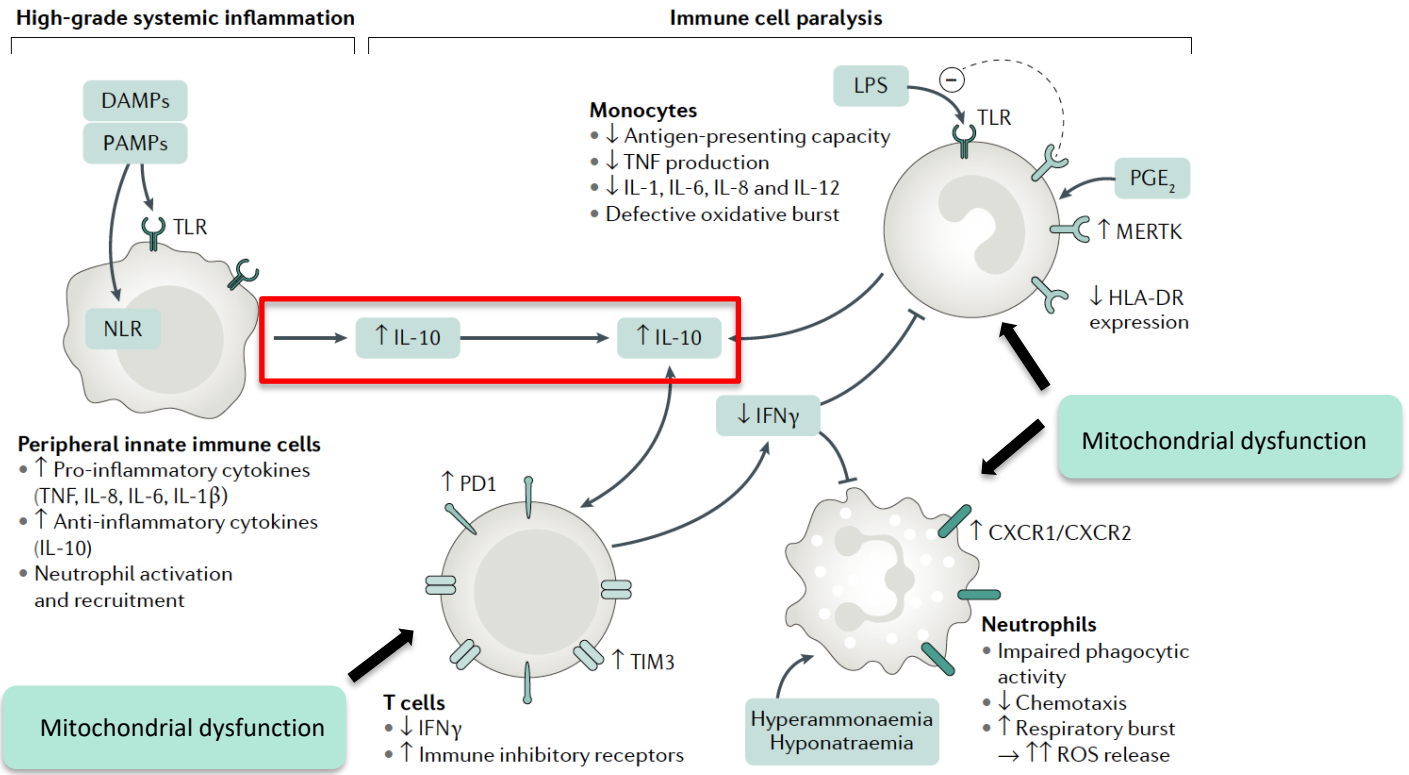


D. I. Williams et al. J. Leukoc. Biol. 2019 ; 106 : 7-9

Immune Dysfunction and ACLF

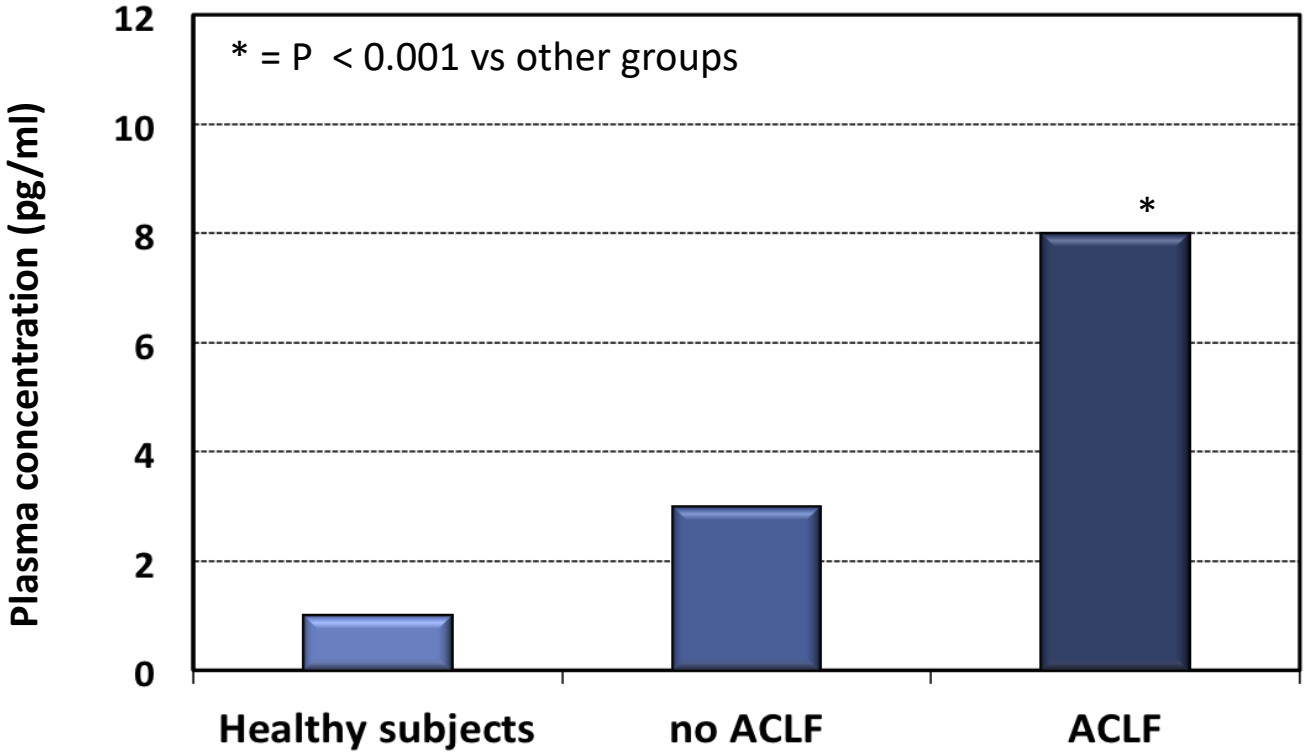
- High grade systemic inflammation
- Upregulation of innate immune response
- Impaired immunemetabolism

Cirrhosis-associated immune-dysfunction



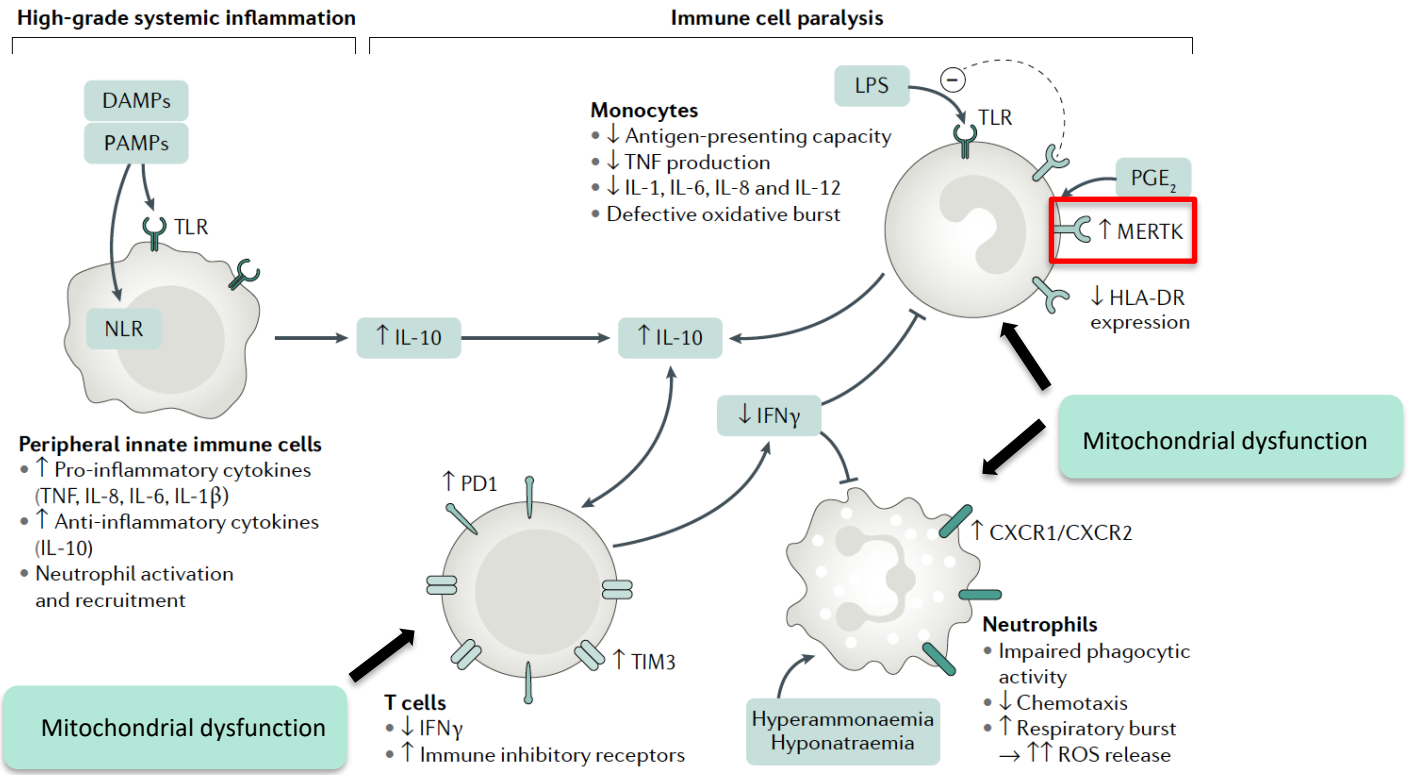
Adapted from A. Albillos et al. et al. Nat. Rev. Gastroenterol. Hepatol. 2022 ; 19 : 112-134

Systemic inflammation in patients with ACLF: IL-10



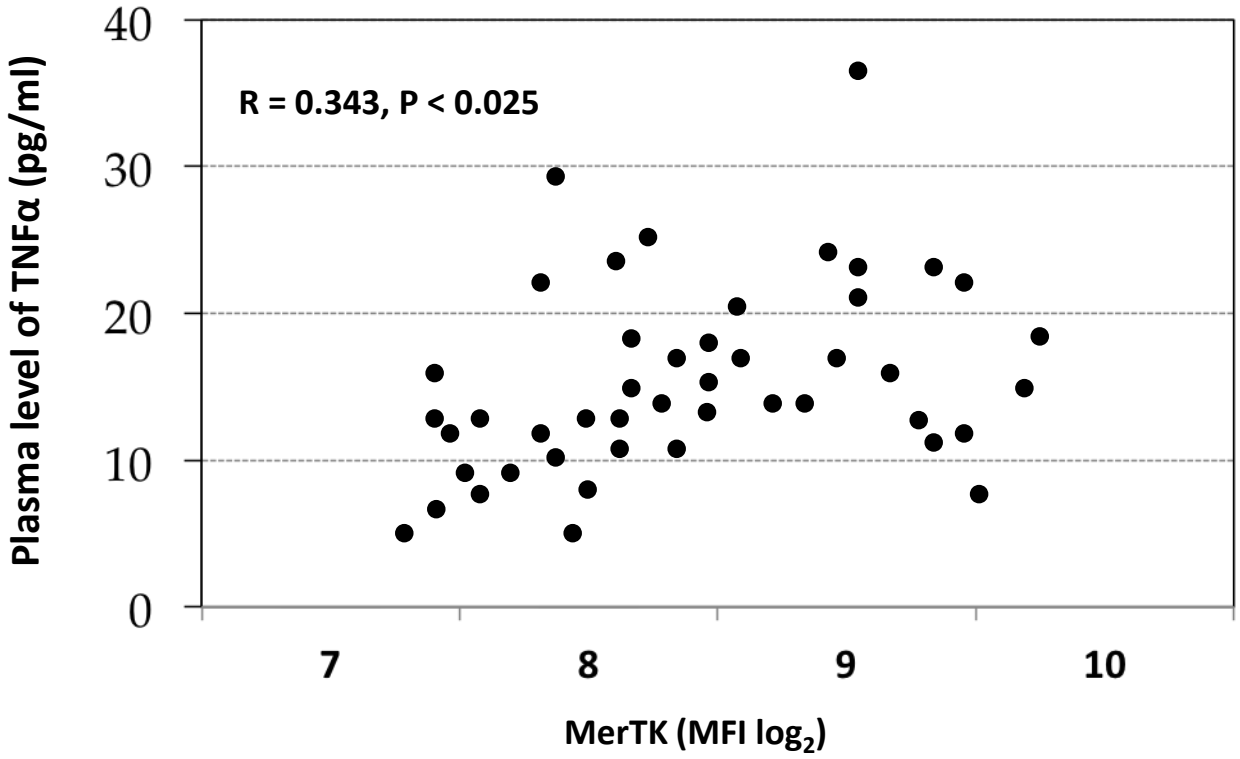
J. Claria et al. Hepatology 2016 ; 64 : 1249-1264

Cirrhosis-associated immune-dysfunction



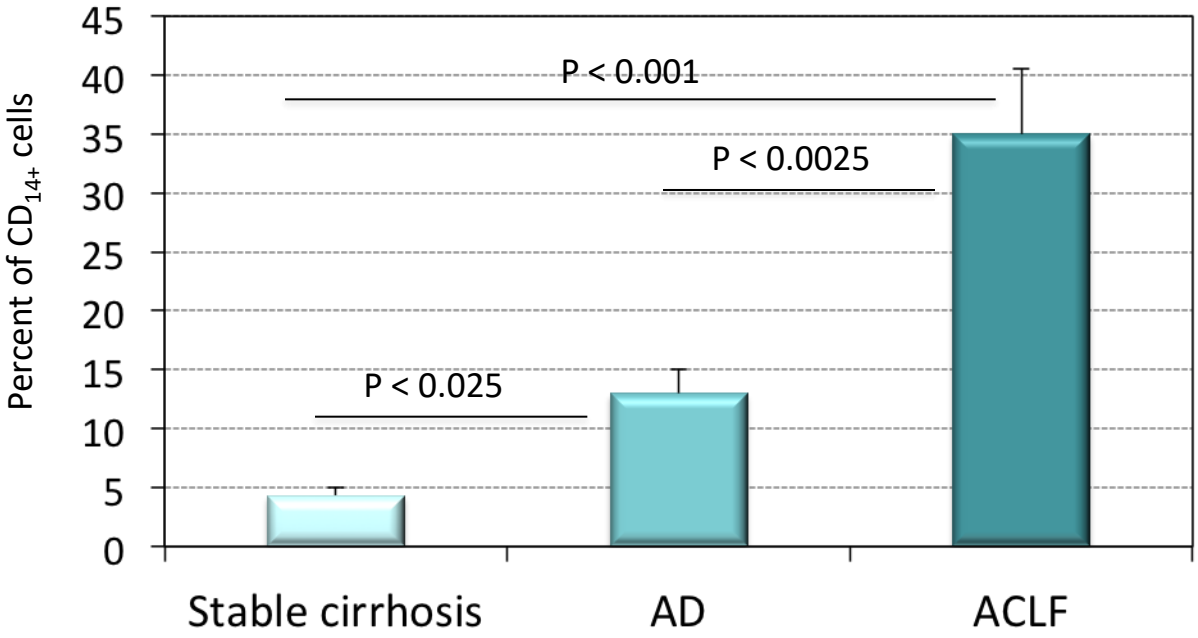
Adapted from A. Albillos et al. et al. Nat. Rev. Gastroenterol. Hepatol. 2022 ; 19 : 112-134

Correlation of plasma TNFα levels of patients with cirrhosis and ACLF with monocyte MERTK expression



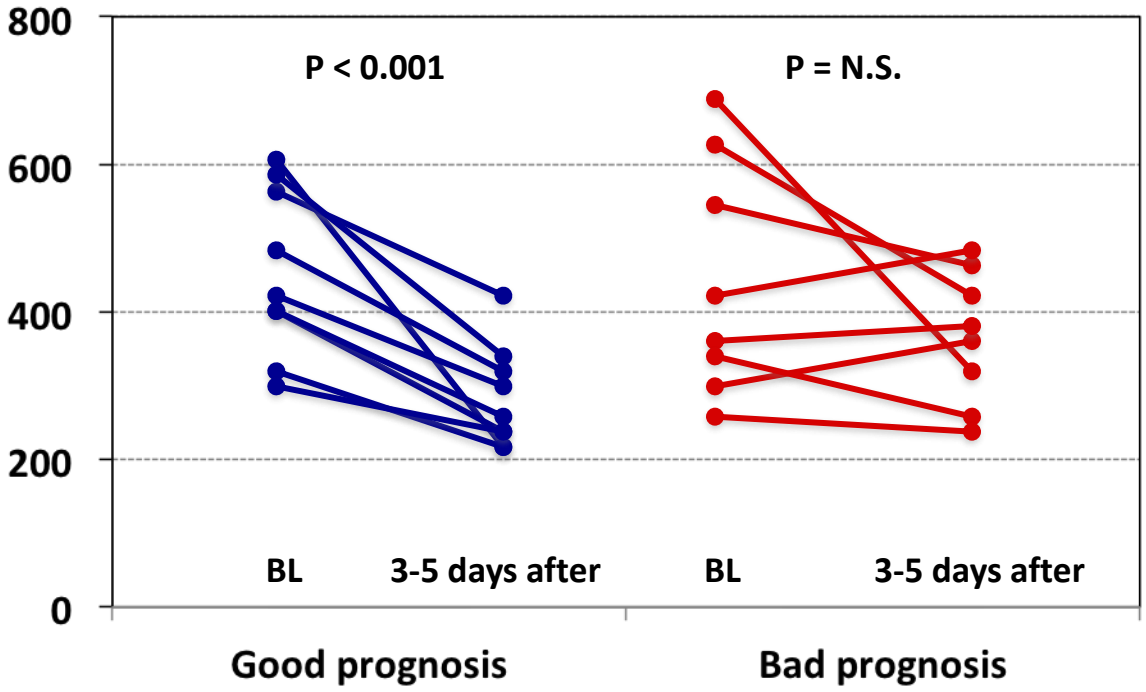
C. Bernsmeier et al. Gastroenterology 2015;148:603–615

MERTK expression in circulatory monocytes in ACLF



C. Bernsmeier et al. Gastroenterology 2015;148:603–615

Sequential MERTK expression in patients with ACLF: at admission (BL, baseline) and 3–5 days after



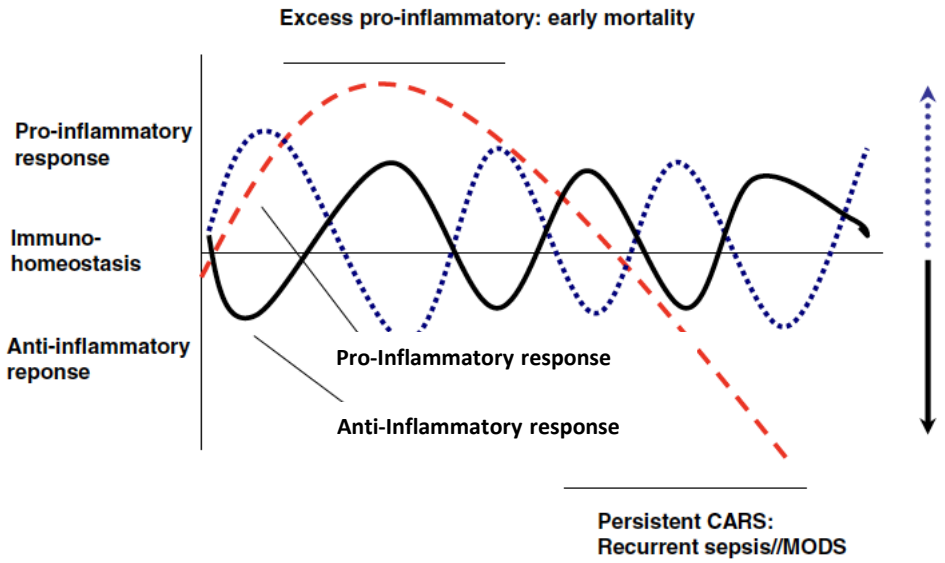
C. Bernsmeier et al. Gastroenterology 2015;148:603–615

TNFα production (A) by peripheral monocyte after stimulation with LPS in study groups

Cytokine	Liver cirrhosis	ACLF (early)	ACLF (late)	P*
TNFα (pg/ml)	1354.8 ± 323.4	2305.4 ± 732.7	1173.1± 513.9	< 0.01
Il-10 (pg/ml)	46.1 ± 11.2	53.9 ± 19.8	78.3 ± 27.4	< 0.01

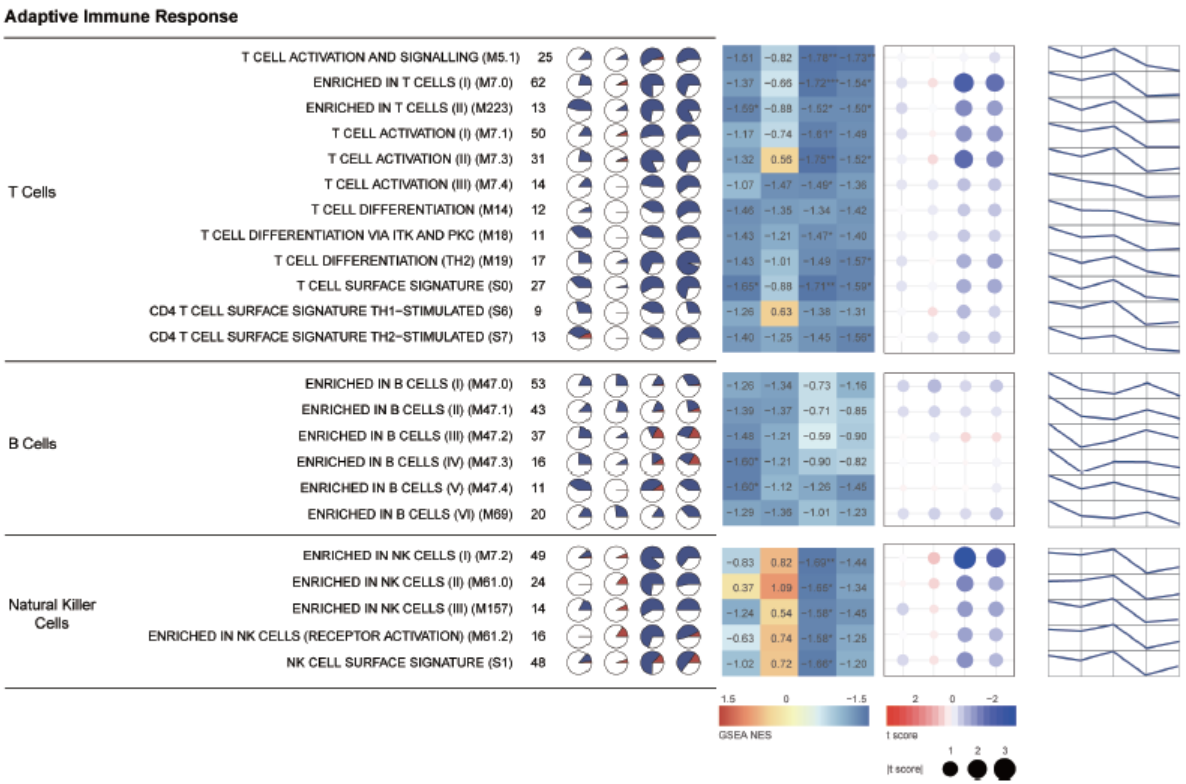
Xing T. et al. Clin. Experim. Immunol. 2006 ; 147 : 184-188

Interaction between the pro-inflammatory (SIRS) and anti-inflammatory (CARS) in the evolution of ACLF



Adapted from C.A. Antoniades et al. J. Hepatol. 2008 ; 49 : 945-861

Downregulation og genes related to adaptive immune response in patients with ACLF



J. Li et al. Gut 2022;71:163–175.

Immune Dysfunction and ACLF

- High grade systemic inflammation
- Upregulation of innate immune response
- Impaired immune metabolism
- Downregulation of adaptive immune response
- Immune paralysis

Main causes of death in patients with acute on chronic liver failure (ACLF)

Causes of Death	Deaths at 28 Days (N=144)	Deaths at 90 Days (N=265)
Organ failure/s	63 (43.8%)	99 (37.4%)
Septic shock	40 (27.8%)	62 (23.4%)
Hypovolemic shock	12 (8.3%)	19 (7.2%)
Cirrhosis *	0	7 (2.6%)
Cerebral hemorrhage	2 (1.4%)	4 (1.5%)
Myocardial infarction	1 (0.7%)	4 (1.5%)
Hepatocellular carcinoma	1 (0.7%)	4 (1.5%)
Non-liver cancer	2 (1.4%)	2 (0.8%)
Massive pulmonary inhalation	1 (0.7%)	2 (0.8%)
Epileptic status	1 (0.7%)	2 (0.8%)
Pulmonary embolism	0	2 (0.8%)
Other causes **	7 (4.9%)	11 (4.2%)
Cause unknown	11 (7.6%)	42 (15.8%)

R. Moreau et al. Gastroenterology 2013 ; 144 : 1426-1437

Agenda

- Pathophysiology of decompensation and organ failures
- Definition of decompensation and ACLF

Major complications in cirrhosis

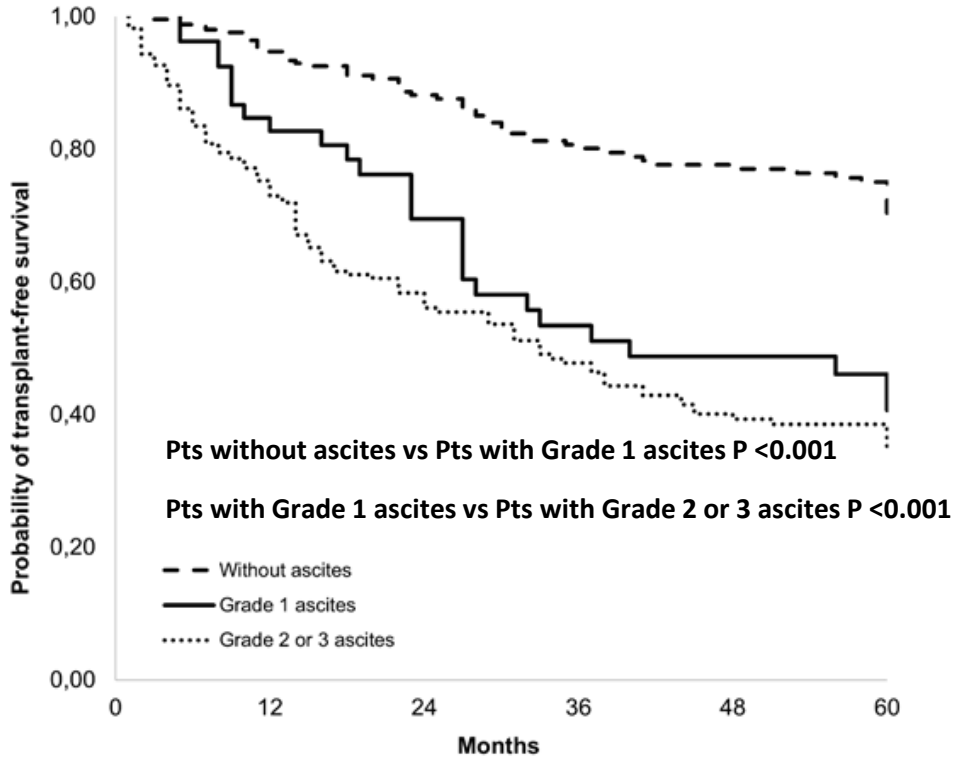
- Ascites
- Hepatic encephalopathy
- Gastrointestinal bleeding
- Extrahepatic organ or system failure/dysfunction
- Jaundice
- HCC
- Bacterial infections (sepsis)
- Sarcopenia
- Osteoporosis

Feature of well-standardized decompensating events in cirrhosis

	High relative prevalence	Specificity	Negative impact on prognosis	Link to pathophysiology
Ascites*	Yes	High	Yes	Yes
Variceal bleeding	Yes	High	Yes	Yes
Hepatic encephalopathy	Yes	High	Yes	Yes
Jaundice	Yes	Medium/High	Yes	Yes

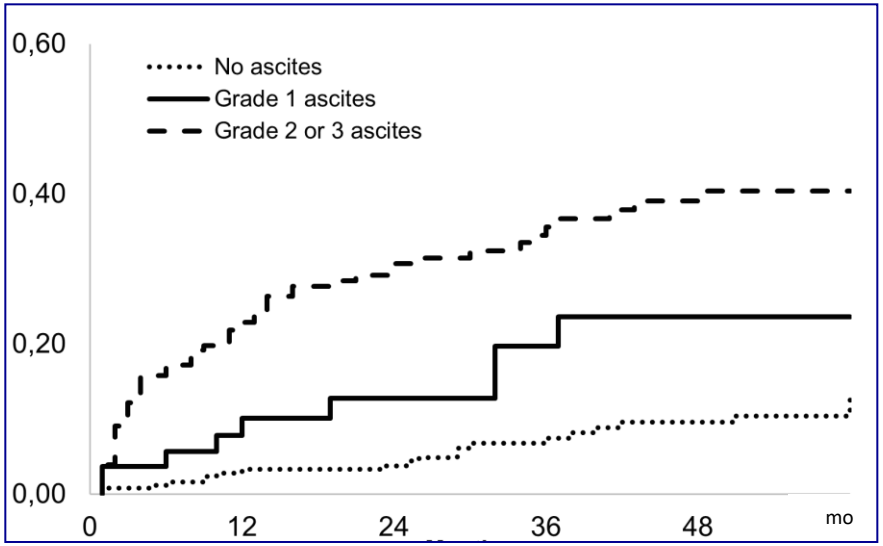
* = this is true also for grade 1 ascites

Probability of survival according to the Grade of ascites



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

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

Feature of well-standardized decompensating events in cirrhosis

	High relative prevalence	Specificity	Negative impact on prognosis	Link to pathophysiology
Ascites*	Yes	High	Yes	Yes
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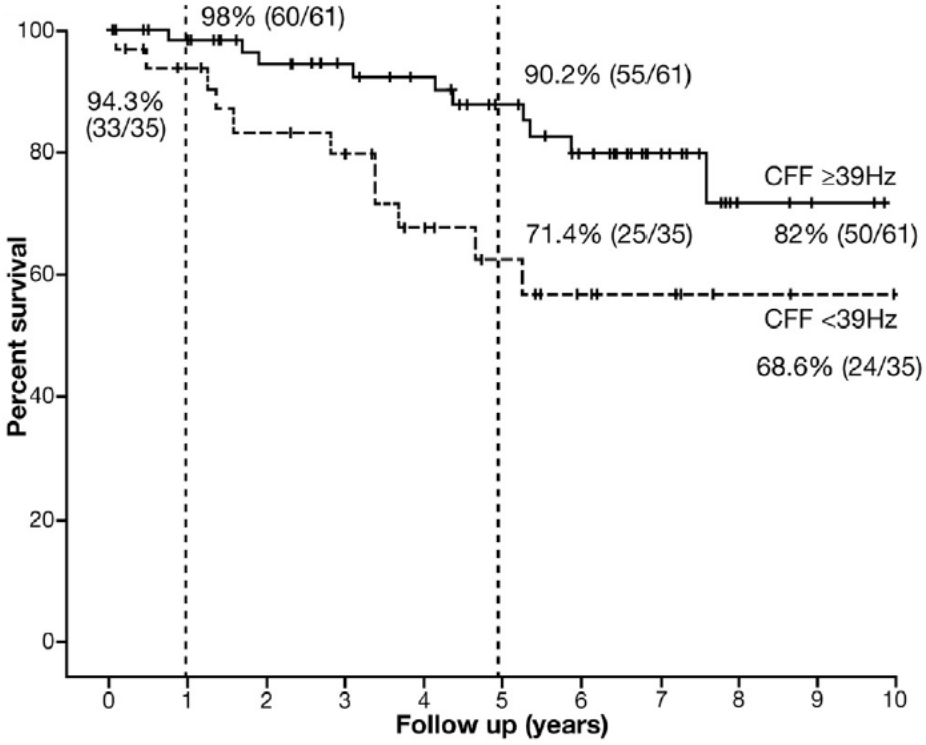
Hepatic encephalopathy*	Yes	High	Yes	Yes
Jaundice	Yes	Medium/High	Yes	Yes

* = this is true also for grade 1 ascites

* = this is true also for covert hepatic encephalopathy

Impact of minimal hepatic encephalopathy (detected by CFF) in cirrhosis

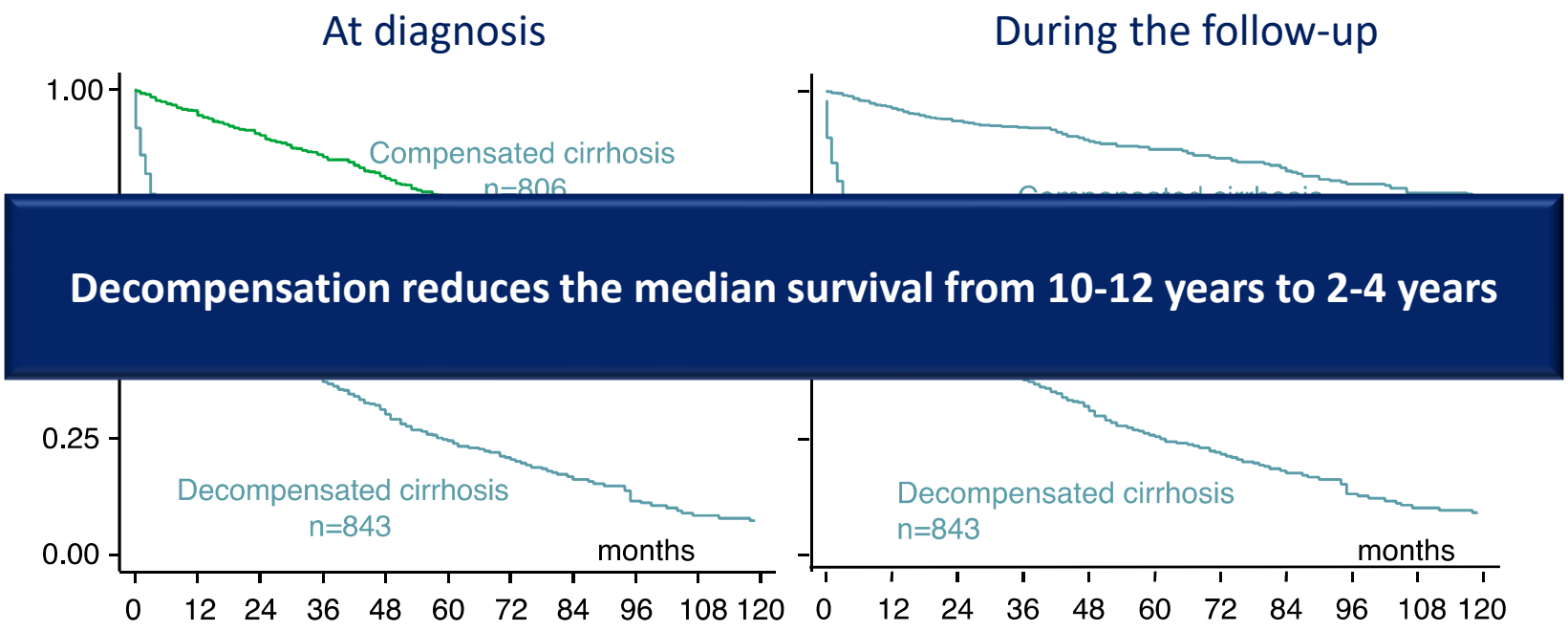


J. Ampuero et al. Gastroenterology 2015 ; 149 : 1483-1489

Crossing the Rubicon

F. Granacci (1477-1543) ; Victoria and Albert Museum : London (UK)

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

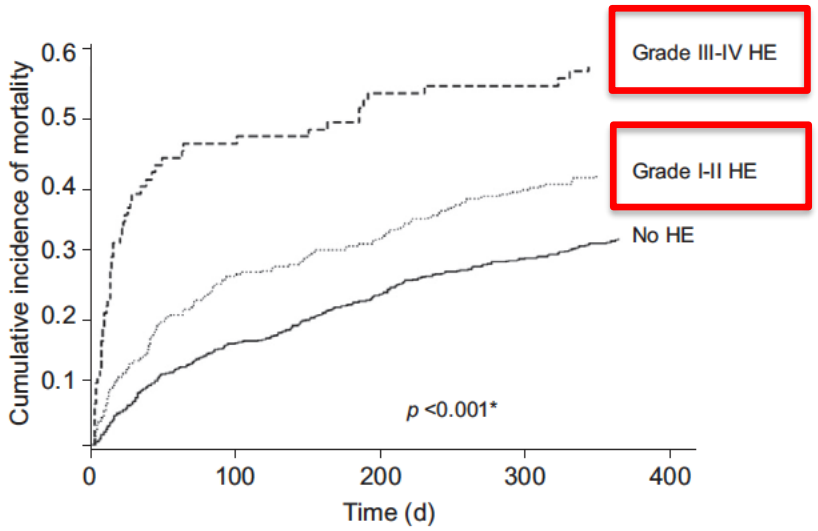
Five year mortality in patients with cirrhosis

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%**
5°	Any second decompensating event	**88%**

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

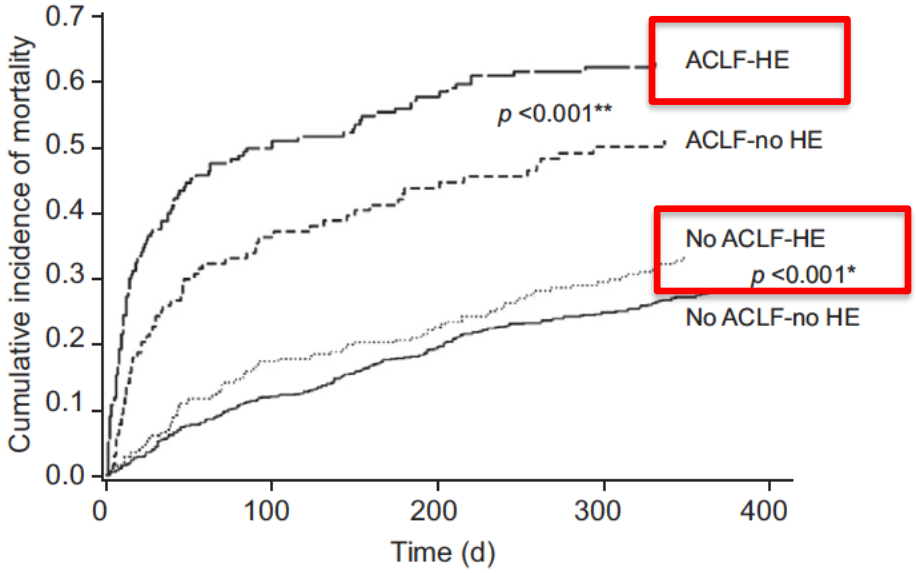
* The study is based on a database drawn from a prospective inception cohort of 554 consecutive patients with a diagnosis of compensated cirrhosis (n° 377) or still decompensated cirrhosis (n° 177) included from June 1981 to June 1984.

Mortality of patients related to the severity of hepatic encephalopathy



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

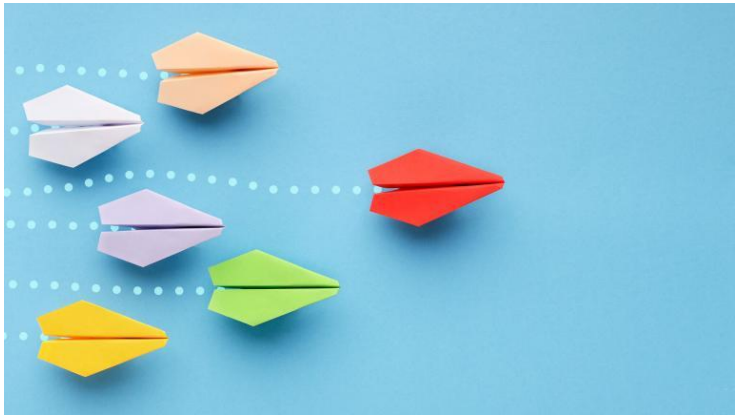
Mortality of patients with hepatic encepalophaty (HE) according to the diagnosis of acute on chronic liver failure (ACLF)



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: further decompensation and acute decompensation (AD).



The Tower of Babel

Pieter Bruegel The Elder, The Tower of Babel, 1563, Kunsthistorisches Museum Vienna

Definition of further decompensation

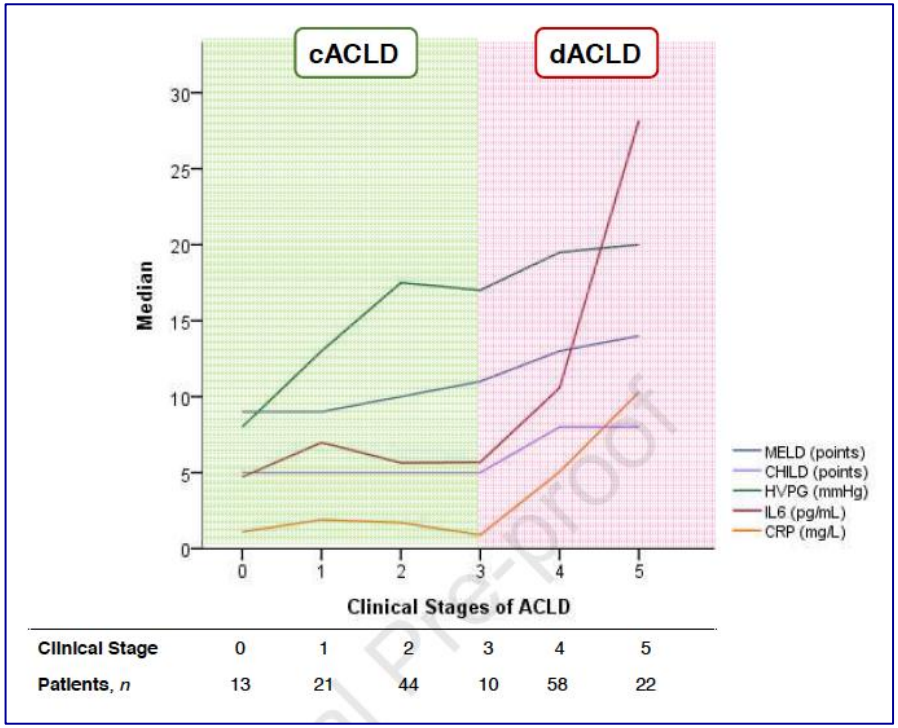
Specific events that define further decompensation are any of the following:

- 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.

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

Definition of further decompensation

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

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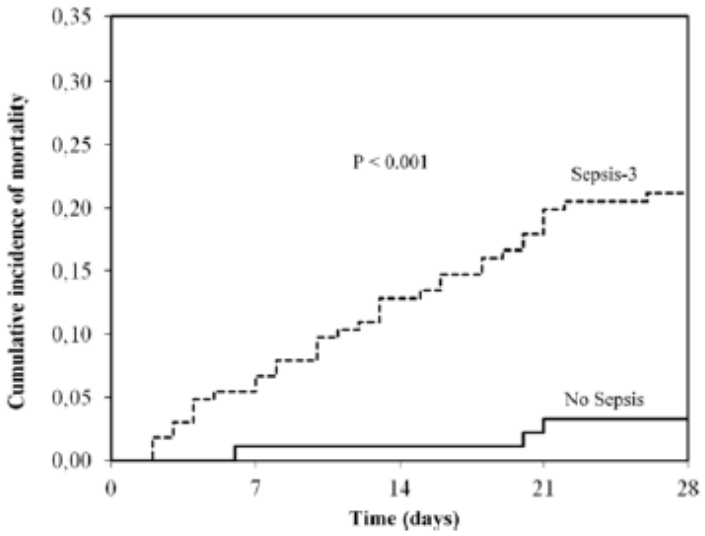
R. De Franchis et al. J. Hepatol. 2022 ; 76 : 959-974

Bacterial infections *versus* othe decompensating events in cirrhosis

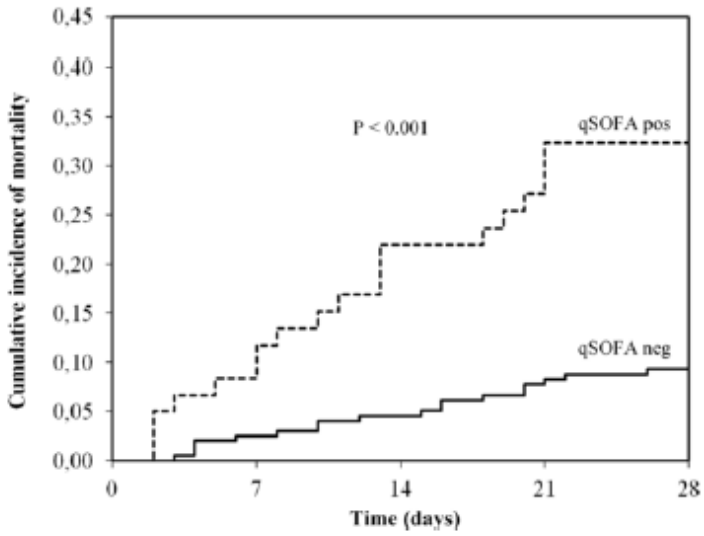
	High relative prevalence	Specificity	Negative impact on prognosis	Link to pathophysiology
Ascites	Yes	High	Yes	Yes
Variceal bleeding	Yes	High	Yes	Yes
Hepatic encephalopathy	Yes	High	Yes	Yes
Jaundice	Yes	Medium	Yes	Yes
Sepsis	**Yes**		**?**	**Yes**

Mortality at 28 days in patients with cirrhosis and sepsis according to positivity of Sepsis 3 (left graph) o sequential positivity of Quick SOFA (right graph)

Mortality at 28 days



Mortality at 28 days

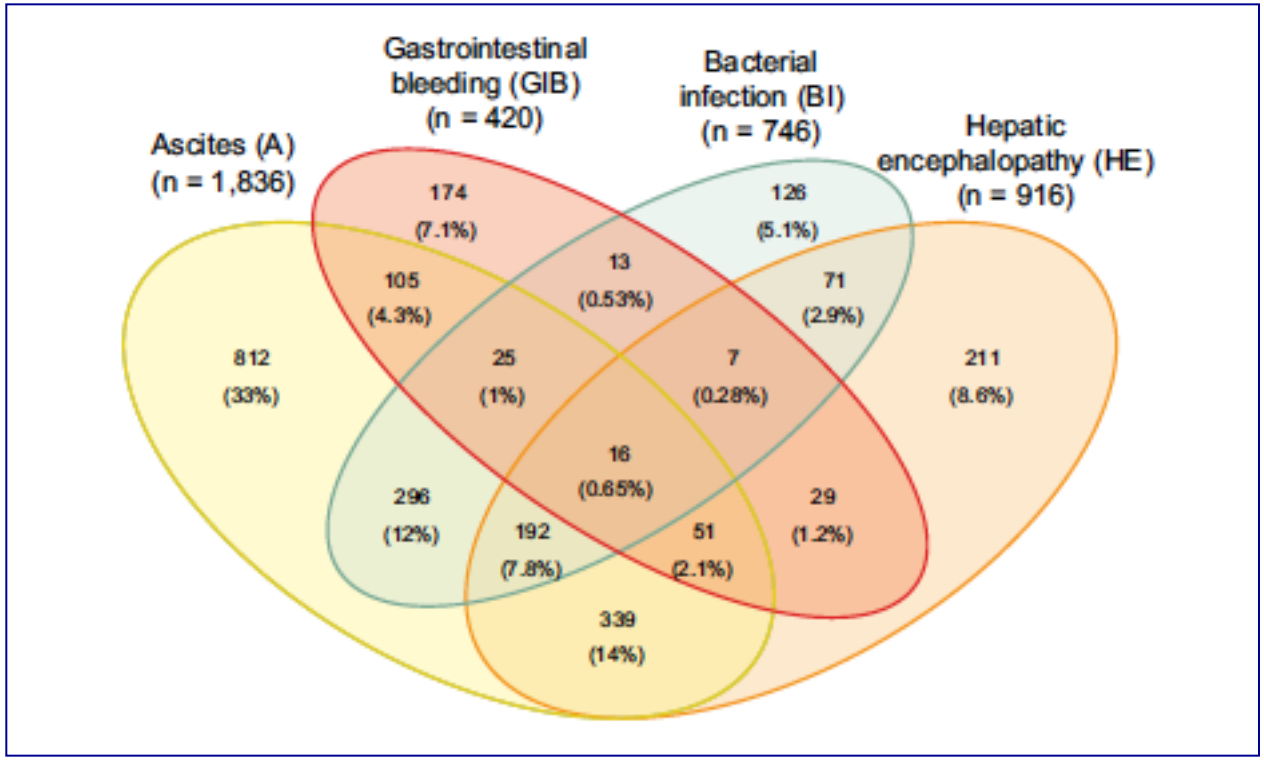


S. Piano et al. Gut. 2018 ; 67 : 1892-1899

Bacterial infections *versus* othe decompensating events in cirrhosis

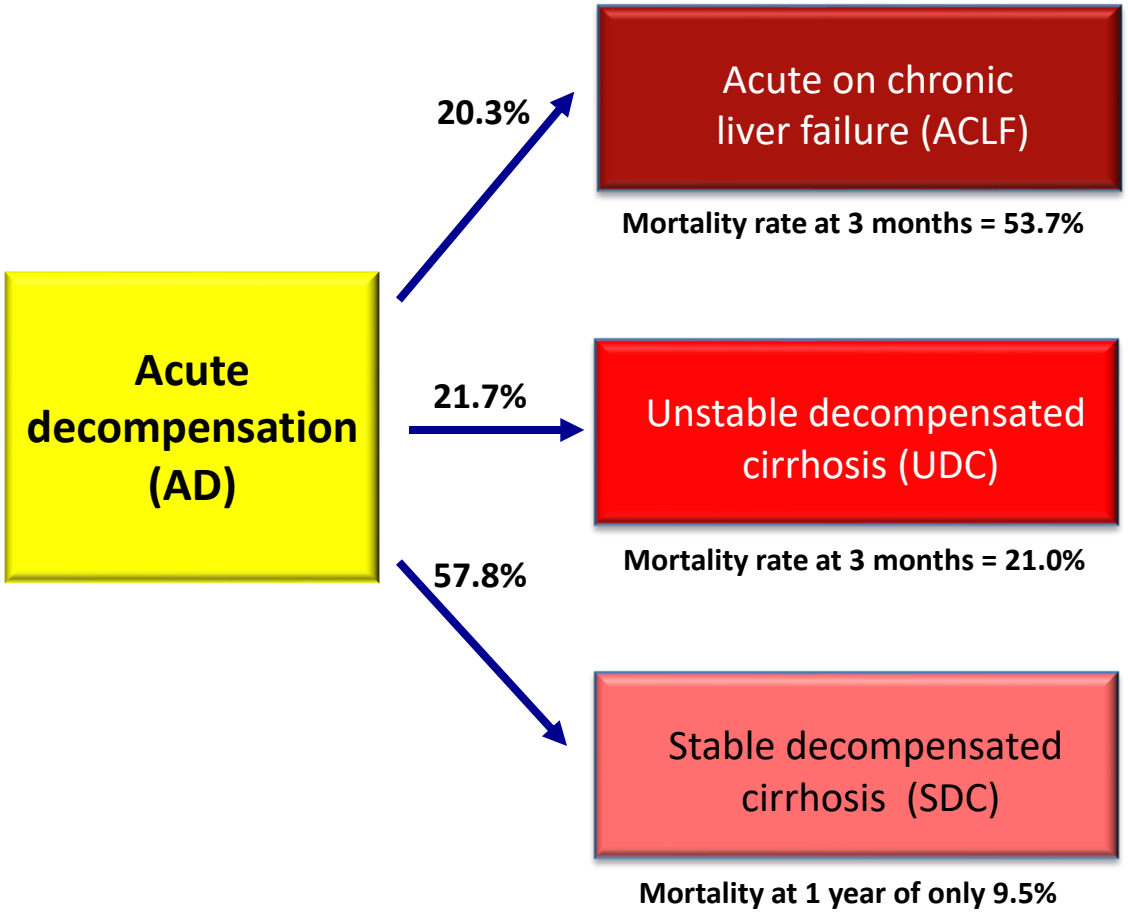
	High relative prevalence	Specificity	Negative impact on prognosis	Link to pathophysiology
Ascites	Yes	High	Yes	Yes
Variceal bleeding	Yes	High	Yes	Yes
Hepatic encephalopathy	Yes	High	Yes	Yes
Jaundice	Yes	Medium	Yes	Yes
Sepsis	**Yes**	**Medium**	**Yes**	**Yes**

Definition of acute decompensation



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

Dynamics and classification of decompensation in patients with cirrhosis



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

EASL CLIF diagnostic criteria

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

R. Moreau et al. Gastroenterology 2013 ; 144 : 1426-1437

Definition of organ failure: the Clif-SOFA score

Organ/system	0	1	2	3	4
Liver (Bilirubin, mg/dl)	< 1.2	≥ 1.2 - ≤ 2.0	> 2 - < 6	≥ 6.0 - < 12	≥ 12.0
Kidney (Creatinine, mg/dl)	< 1.2	≥ 1.2 - < 2.0	≥ 2.0 - < 3.5	≥ 3.5 - < 5.0	≥ 5.0
			or use of RRT		
Cerebral (HE grade)	No HE	Grade I	Grade II	Grade III	Grade IV
Coagulation (INR)	< 1.1	≥ 1.1 - < 1.25	≥ 1.25 - < 1.5	≥ 1.5 - < 2.5	≥ 2.5 or platelets ≤ $20x10^9$/l
Circulation (MAP, mm Hg)	≥ 70	< 70	Dopamine ≤ 5 µg/kg/min or Dobutamine or Terlipressin	Dopamine > 5 µg/kg/min or E ≤ 0.1 or NE ≤ 0.1 µg/kg/min	Dopamine > 15 µg/kg/min or E > 0.1 or NE > 0.1 µg/kg/min
Lungs (PaO_2/FiO_2) or (SpO_2/FiO_2)	> 400	> 300 - ≤ 400	> 200 - ≤ 300	> 100 - ≤ 200	≤ 100
	> 512	> 357 - ≤ 512	> 214 - ≤ 357	> 8 - ≤ 214	≤ 89

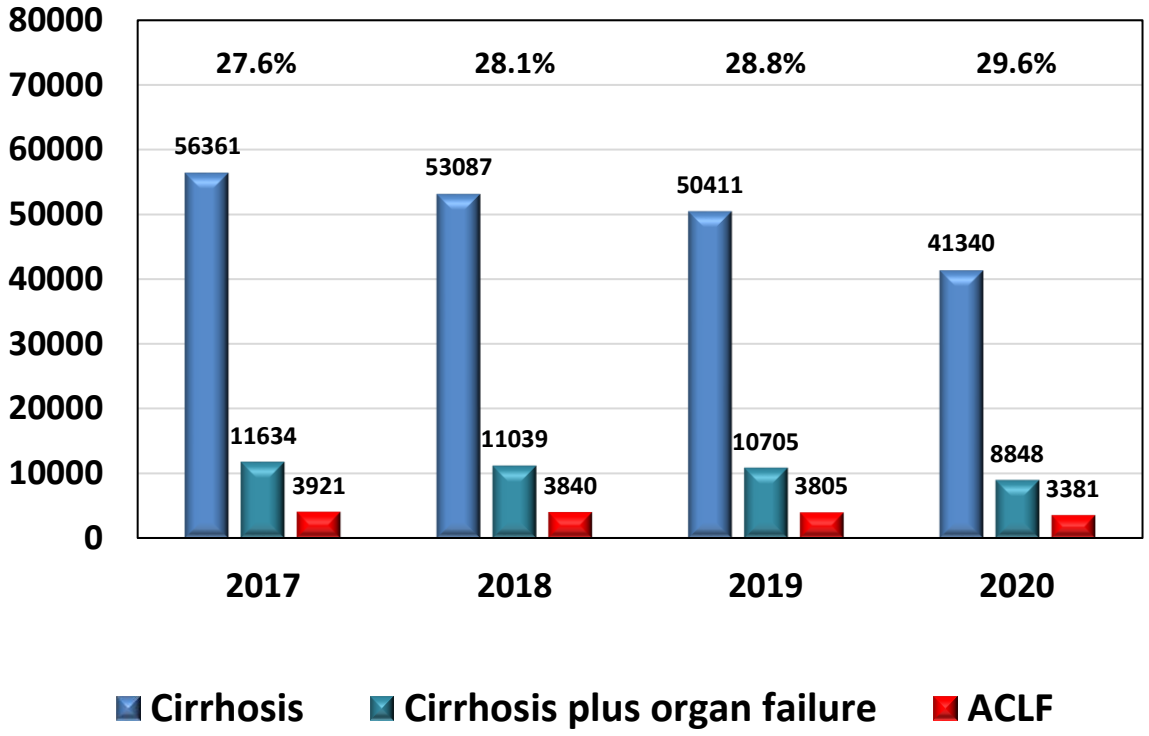
R. Moreau et al. Gastroenterology 2013 ; 144 : 1426-1437

Acute on chronic liver failure (ACLF)

Grade of ACLF	28 day mortality	90 day Mortality
Grade 1-Type a : patients with single kidney failure Grade 1-Type b: patients with one "non-kidney" organ failure but with serum creatinine ranging from 1.5 to 1.9 mg/dL and/or mild-to moderate-hepatic encephalopathy	22.1 %	40.7 %
Grade 2: patients with two organ failures	32.0 %	52.3 %
Grade 3: patients with three or more organ failures	76.7 %	79.1 %

R. Moreau et al. Gastroenterology 2013 ; 144 : 1426-1437

Absolute number of hospitalizations for cirrhosis and ACLF in Italy



Data received from Ministery of Health (2024)

Economic impact of cirrhosis and ACLF compared to the most common medical conditions requiring hospitalization in US in 2010

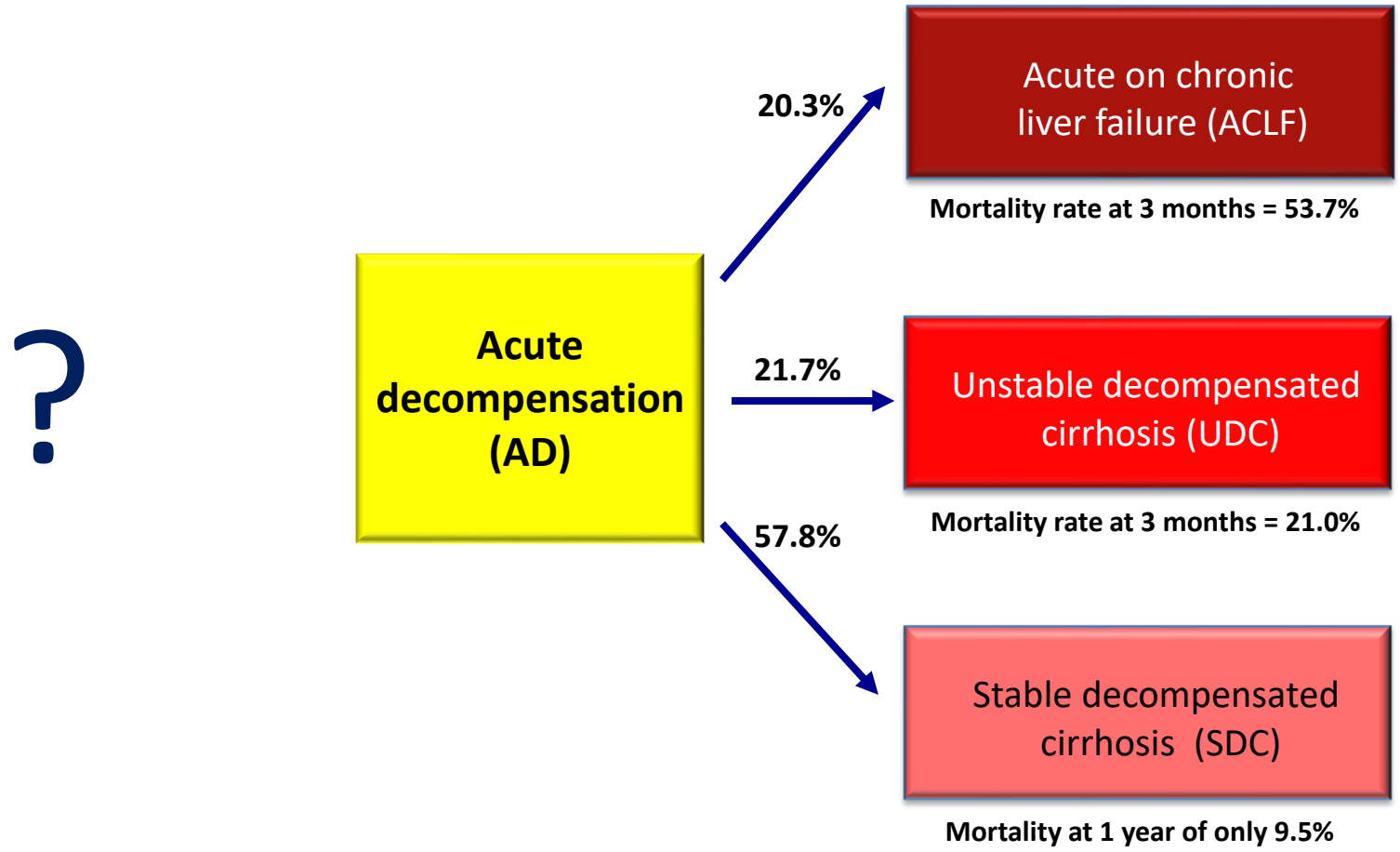
Chronic Disease	N° of hospitalization	Leght of hospital stay	Inpatient mortality	Mean cost per hospitalization
Cirrhosis	606,288	7	7.5%	$ 15.732
ACLF	28,637	16	53.3%	$ 54,727
Sepsis	808,000	9	16.3%	$ 15,467
Pneumonia	1.1 milion	5	3.3%	$ 7,581
Congestive heart disease	1 milion	5	3.0%	$ 8,315
Cerebrovascular disease	1 milion	6	4.7%	$ 8,117

AM. Allen et al. Hepatology 2016 ; 64 : 2165-2172

Agenda

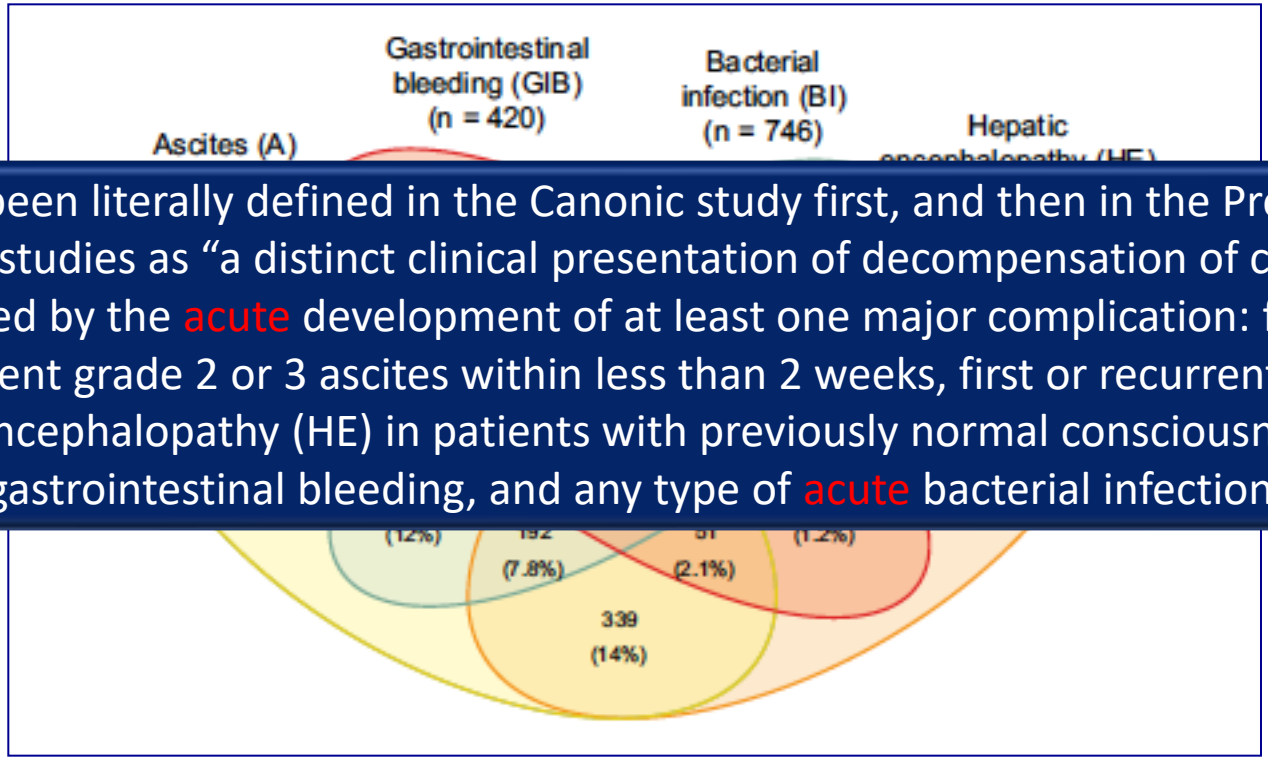
- Pathophysiology of decompensation and organ failures
- Definition of decompensation
- Different phenotypes of decompensation

Dynamics and classification of decompensation in patients with cirrhosis



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

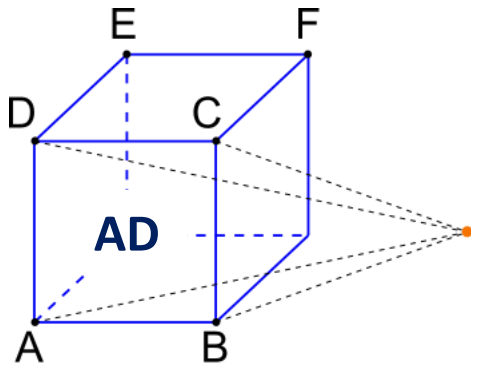
Definition of acute decompensation



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”

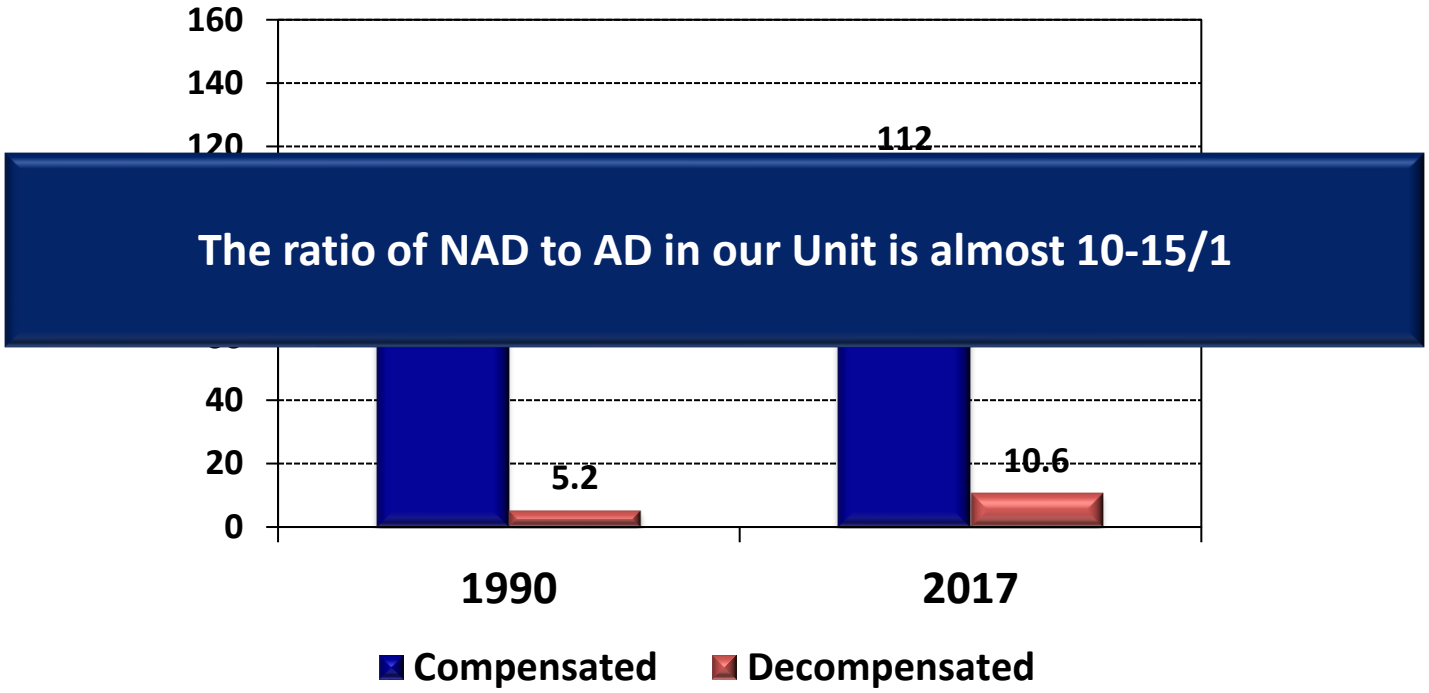
V. Arroyo et al. J. Hepatol. 2021 ; 74 : 670-685

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

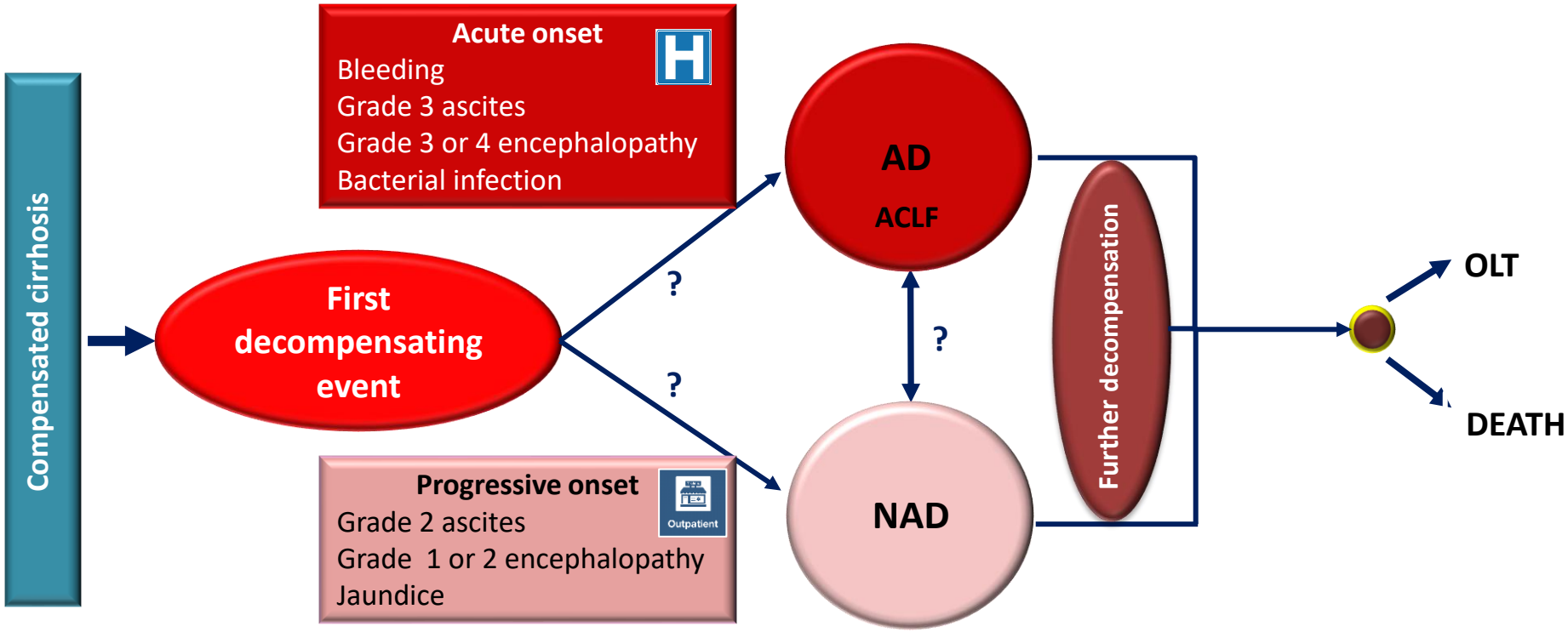
Lancet 2020 ; 5 : 245-266

New classification of decompensation in cirrhosis

- **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.

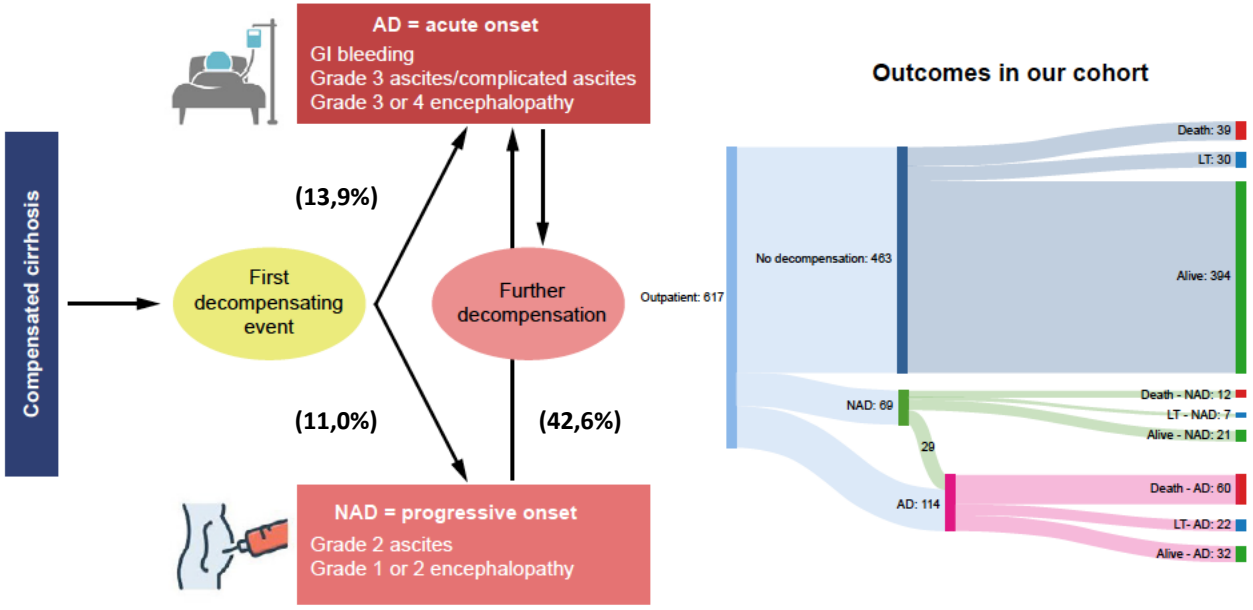
- **NAD** occurs mostly as a single, progressive and mild decompensating event (ascites, encephalopathy) and, usually, does not require hospitalisation.

New definition of decompensation in patients with cirrhosis



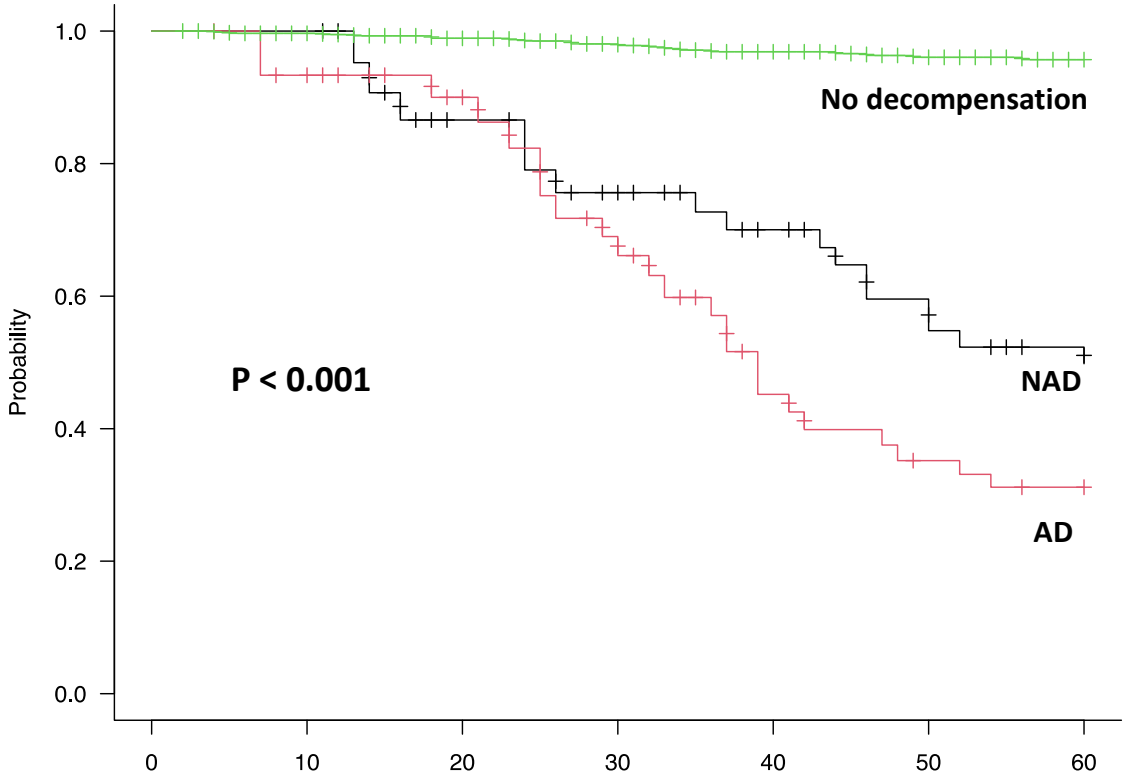
Adapted from G. D'Amico et al. J Hepatol. 2022 ; 76 : 202-207

Dynamics and classification of decompensation in patients with cirrhosis



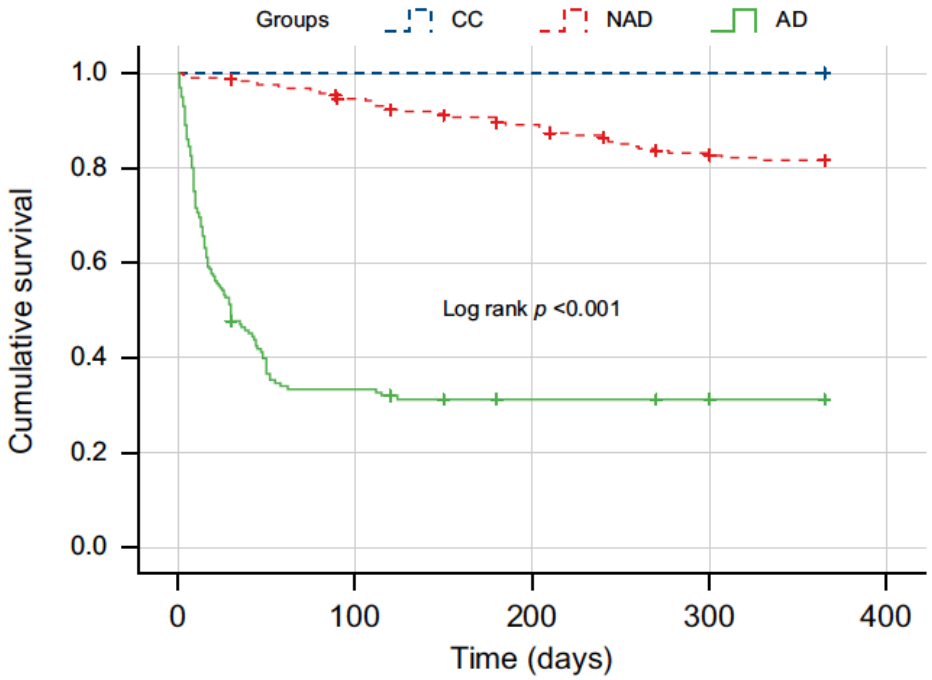
M. Tonon et al. J Hepatol. 2024 ; 80 : 603-609

Probability of survival according to the type of decompensation



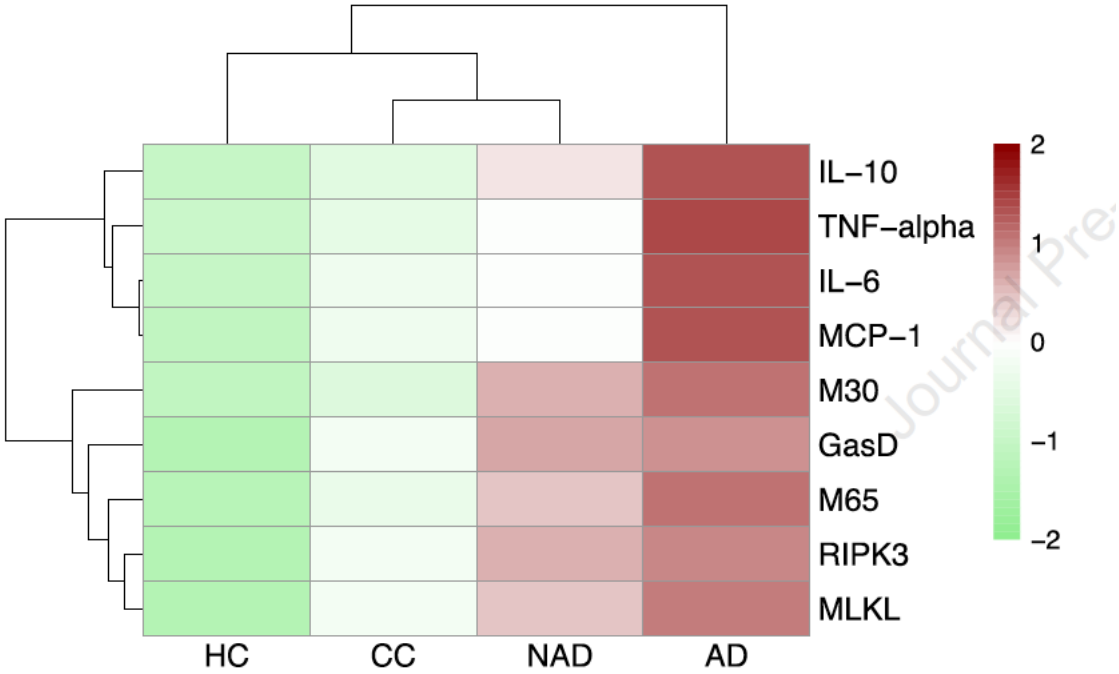
M. Tonon et al. J Hepatol. 2024 ; 80 : 603-609

Probability of 12-month survival in patients with compensated cirrhosis (CC), and in patients with non-acute (NAD), or acute (AD) decompensation



N. Verma et al. J Hepatol 2025 ; 83 : 670-681

Pathophysiological profile in patients with cirrhosis: NAD versus AD



N. Verma et al. J Hepatol 2025 ; 83 : 670-681

Take away messages

- Decopensating events have a deep negative impact on survival in patients with cirrhosis.
- The current definitions of decompensation in patients with cirrhosis must be updated, refined and harmonized.
- The first decompensating event in patients with cirrhosis can develops with two patterns: non acute decompensation (NAD) and acute decompensation (AD).
- More than fourty percent of the patients who developed NAD then develop AD.
- Systemic Inflammation (**SI**) is an early processs in patients with cirrhosis.
- Bacterial transplocation and liver cell death are its main sources.
- Precipitating events increase the degree of **SI** and contribute to defining its profile.
- **SI** is a powerful driver of decompensation, organ failures and ACLF but many aspects related to SI in this context are still unclear.