L'ACLF: conoscerla per minimizzarla

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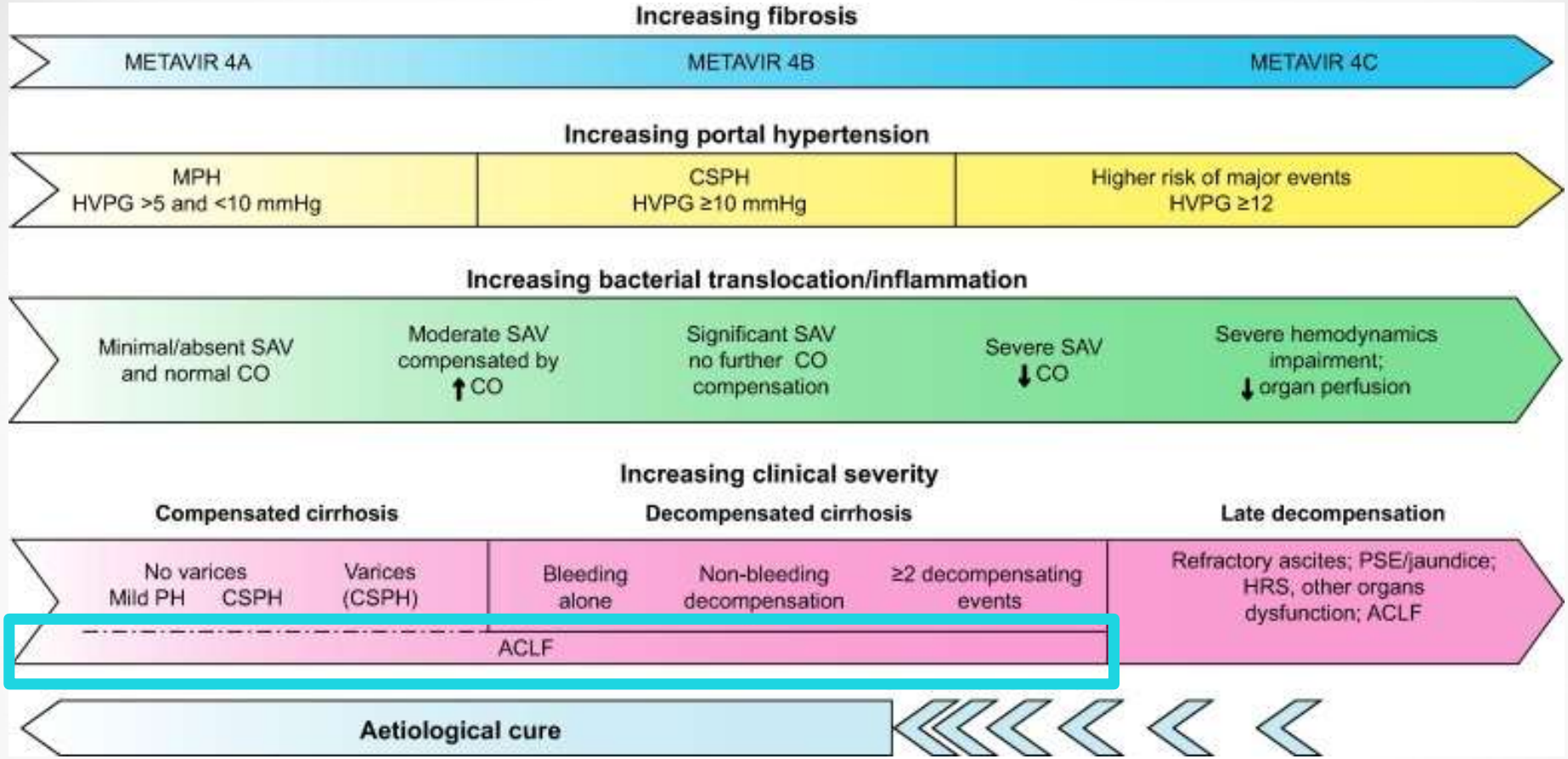
Agenda

- Definition/s of ACLF and epidemiology
- Pathophisiology
- Therapeutic
- PRE-ACLF
- The role of liver transplant in the management of ACLF



D'Amico et al. J Hepatol 2018

Epidemiology of definitions of ACL

More than 13 distinct definitions of ACLF have been proposed. Among them are the following:

- The Asian Pacific Association for the Study of the Liver Diseases (APASL) definition (2004-2014)
- The European Association for the Study of the Liver (EASL) definition (2013)
- The EASL-Clif Consortium definition
- Jalan amd Williams definition (2002)
- The Chinese Medical Association definition (2013)
- The American Association for the Study of the Liver (AASLD) and EASL definition (2012)
- The North-American Consortium for the Study of End Stage Liver Disease definition (2014)
- The World Gastroenterology Organization Working Party definition (2014)

Adapted from V. Arroyo et al. Nat. Rev. Dis. Primers 2016

Definition of acute on chronic liver failure

- In the Canonic study, an European prospective observational study, 1343 hospitalized cirrhotics with AD , were enrolled
- Acute decompensation (AD) was defined by the acute development of one major complication of liver disease (i.e., ascites, encephalopathy, gastrointestinal hemorrhage, bacterial infection) or more.
- Diagnostic criteria of ACLF were obtained after identifying subgroups of patients with both:
  - organ failure/s, defined by the chronic liver failure (CLIF)-SOFA score

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

In 2009, th APASL provided the first consensus on ACLF, defined as «**an acute hepatIc insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascite and/or encephalopathy**». The 2014 definition was futher expanded to include '**high 28-day mortality**'

	APASL	EASL/CLIF
Definition	Acute hepatic insult manifesting as jaundice (serum bilirubin ≥ 5 mg/dL and coagulopathy (INR ≥ 1.5) complicated within 4 weeks by clinical ascites and/or encephalopathy in a pt with previously DX or undiagnosed CLD/cirrhosis, and is a/with a high 28-day mortality.	An acute deterioration of pre-existing CLD usually related to a precipitating event and a/with ↑ mortality at 3 months due to MOF
Study cohort	First consensus was the expert opinion, subsequently prospectively evaluated in 1402 pt, subsequently in 3300 pts.	Prospectively studied in 1343 pts
Inclusion	• Compensated Cirrhosis (DX or non-diagnosed) • CLD but not cirrhosis • Acute insult directed to liver • **Presentation with liver failure**	• Cirrhosis only • Compensated or **decompensated** • **Renal failure is mandatory** (not liver failure for defining ACLF) • Presentation not necessarily be liver failure

Patients with **cirrhosis** with **acutely decompensated cirrhosis** and **organ failures** (including extrahepatic), that are based on a modified Sequential Organ Failure Assessment score, the chronic liver failure organ failure (CLIF–OF) score. The **CLIF–OF score** considers **six different organ systems** that can fail in ACLF (**liver, kidney, brain, coagulation, circulation and respiration**). Moreover, this definition considers patients with cirrhosis regardless of the presence of prior decompensations.

According to the number of organ failures, patients with ACLF are stratified into three groups with progressively increasing risk of mortality:
ACLF grade 1 (single kidney failure or another single organ failure when associated with brain or kidney dysfunction);
ACLF grade 2 (two organ failures)
ACLF grade 3 (three or more organ failures)

Definition of acute on chronic liver failure

- In the **Canonic study**, an European prospective observational study, **1343 hospitalized cirrhotics with AD** , were enrolled
- Acute decompensation (**AD**) was defined by the acute development of one major complication of liver disease (i.e., **ascites, encephalopathy, gastrointestinal hemorrhage, bacterial infection**) or more.
- **Diagnostic criteria of ACLF were obtained after identifying subgroups of patients with both**:
  - **organ failure/s**, defined by the chronic liver failure (CLIF)-SOFA score
  - **high 28-day mortality (>15%).**

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

Definition of organ failure: the Clif-SOFA score

Table 1. The Chronic Liver Failure (CLIF)-Sequential Organ Failure Assessment (SOFA) Score

Organ/system	0	1	2	3	4
Liver (Bilirubin, mg/dL)	<1.2	≥1.2 - ≤2.0	≥2.0 - <6.0	≥6.0 - <12.0	≥12.0[a]
Kidney (Creatinine, mg/dL)	<1.2	≥1.2 - <2.0	≥2.0 - <3.5[b]	≥3.5 - <5.0 or use of renal-replacement therapy	≥5.0
Cerebral (HE grade)	No HE	I	II	III[c]	IV
Coagulation (INR)	<1.1	≥1.1 – <1.25	≥1.25 - <1.5	≥1.5 – <2.5	≥2.5 or Platelets≤20x10^9/L[d]
Circulation (MAP mm Hg)	≥70	<70	Dopamine ≤5 or Dobutamine or Terlipressin[e]	Dopamine >5 or E ≤ 0.1 or NE ≤ 0.1	Dopamine >15 or E > 0.1 or NE > 0.1
Lungs PaO/FiO2:	>400	>300 - ≤400	>200 - ≤300	>100 - ≤200	≤100
or SpO2/FiO2	>512	>357 - ≤512	>214 - ≤357	>8 - ≤214[f]	≤89

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

	EASL-CLIF consortium	NACSELD	APASL-AARC
Stage of liver disease	Cirrhosis (either compensated or decompensated)	Cirrhosis (either compensated or decompensated)	Chronic liver disease or compensated cirrhosis
Precipitants	Intrahepatic and/or extrahepatic (more common: bacterial infections, severe alcohol-related hepatitis)	Intrahepatic and/or extrahepatic (more common: bacterial infections)	Intrahepatic only (severe alcohol-related hepatitis, HBV reactivation)
Organ Failures	Liver - Kidney - Brain - Coagulation - Circulation - Respiratory (criteria defined per CLIF-OF score)	Kidney - Brain - Circulation - Respiration	Liver (bilirubin ≥5 mg/dL) - Coagulation (INR ≥1.5)
Criteria for ACLF	Acute decompensation of cirrhosis AND single kidney failure OR Every other single organ failure + either kidney dysfunction, brain dysfunction or both OR two or more organ failures	Acute decompensation of cirrhosis AND two or more organ failures	Liver failure AND Coagulation failure + Ascites, HE or both within 4 weeks
Mortality	28-day mortality 22% in Grade 1 32% in Grade 2 77% in Grade 3	30-day mortality 49% in Grade 1 64% in Grade 2 77% in Grade 3	30-day mortality 13% in Grade 1 45% in Grade 2 86% in Grade 3

CLIF-C ACLF (Acute-on-Chronic Liver Failure) score and expected mortality rates

ACLF Grade, CLIF-C OF (Organ Failure) Score and CLIF-C ACLF (ACLF patients) or CLIF-C AD Score (non-ACLF patients with Acute Decompensation)

See score formula

	DATA	CLIF-C Organ Failure Sub-scores
Bilirubin	mg/dl	Liver score Liver failure Yes No
Creatinine Renal replacement therapy	mg/dl Yes No	Kidney score Renal failure Yes No
West-Haven grade for HE	0 1 2 3 4	Brain score Cerebral failure Yes No
INR		Coagulation score Coagulation failure Yes No
MAP Use of vasopressors (Circulatory failure indication)	mmHg Yes No	Circulatory score Circulatory failure Yes No
Select one: PaO_2 (preferred) SpO_2 FiO_2 Mechanical Ventilation	mmHg % % Yes No	Lung score Respiratory failure Yes No
		Total Number Failures CLIF Organ Failure Score
		ACLF Grade

RESET COMPUTE

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"		
Four hundreds and fifteen patients (30.9%) had ACLF ; 303 pts at enrolment, 112 pts during the hospital stay. Nine hundreds and twenty-eight patients did not have ACLF.		
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

Difference in the APALS and EASL-Clif definitions of ACLF

Feature	APALS Definition	EASL-Clif Definition	NACSELD Definition
Criteria	Jaundice and coagulopathy, and within 4 wks ascites and/or HE	Hepatic and extrahepatic organ failure/s	Extra-hepatic organ failures
Time between insult and ACLF	4 wks	Not defined	Not defined
Interval in which there is an high mortality	Not defined	28 days and 3 months	30 days
What qualifies as "chronic liver disease (CLD"	CLD with or without chirrosis	Cirrhosis	Cirrhosis
What qualifies as precipitants ?			
• Alcohol, drugs, hepatotropic viruses, and surgery	Yes	Yes	Not considered
• Bacterial infections	No	Yes	Yes
• Variceal bleeding	Yes	Yes	Not considered

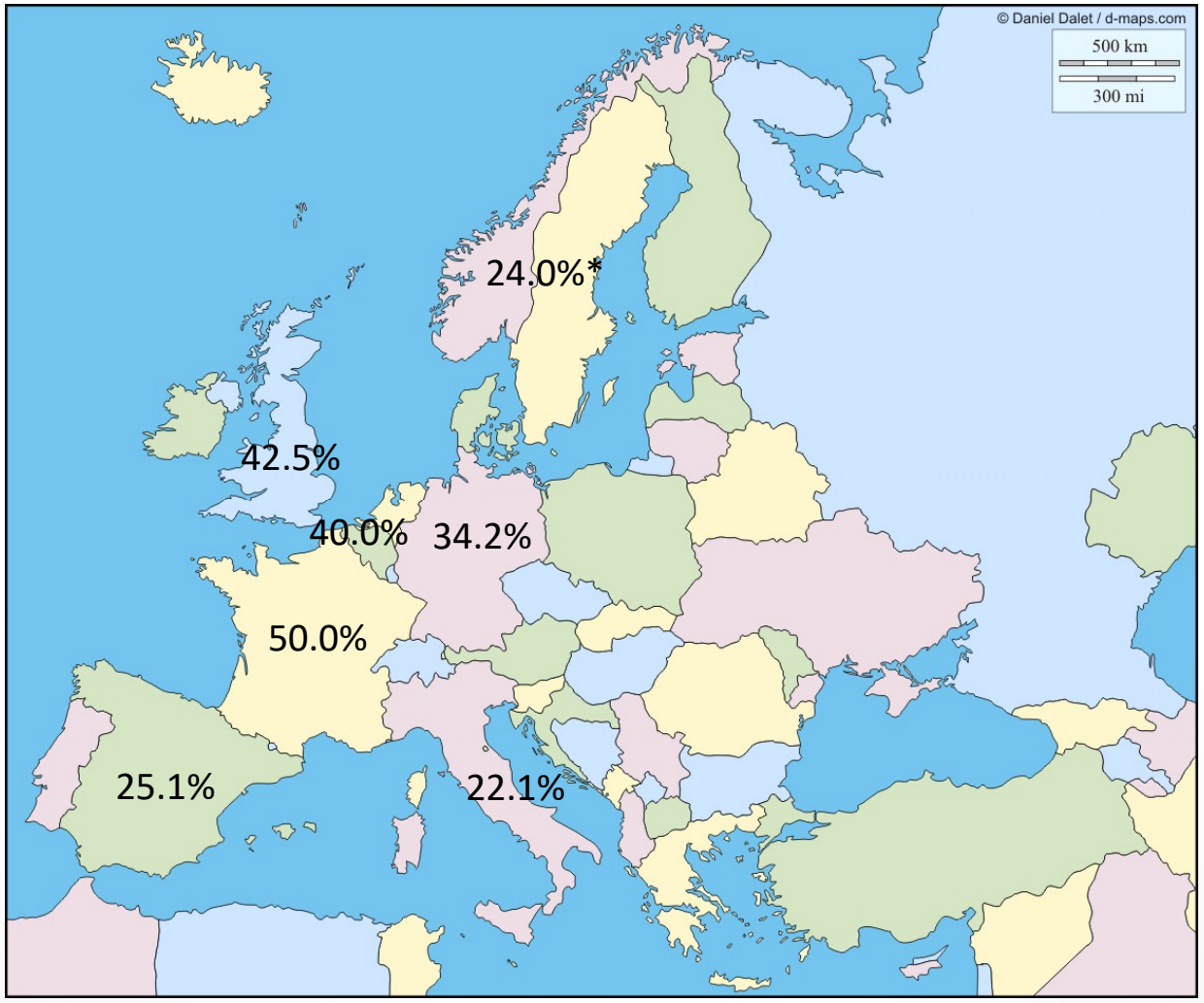
Adapted from JS Bajaj Gastroenterology 2013 ; 144 : 1337-1339

Prevalence of ACLF

- More than 13 distinct definitions of ACLF have been proposed. These definitions are generally based on personal experience or consensus agreements.
- The lack of a universal definition hampers the epidemiologic studies of ACLF.
- Nevertheless, most of the prevalence and natural history data comes from the CANONIC (CLIF Acute on Chronic Liver Failure in Cirrhosis) study,

Prevalence of ACLF in Western Europe

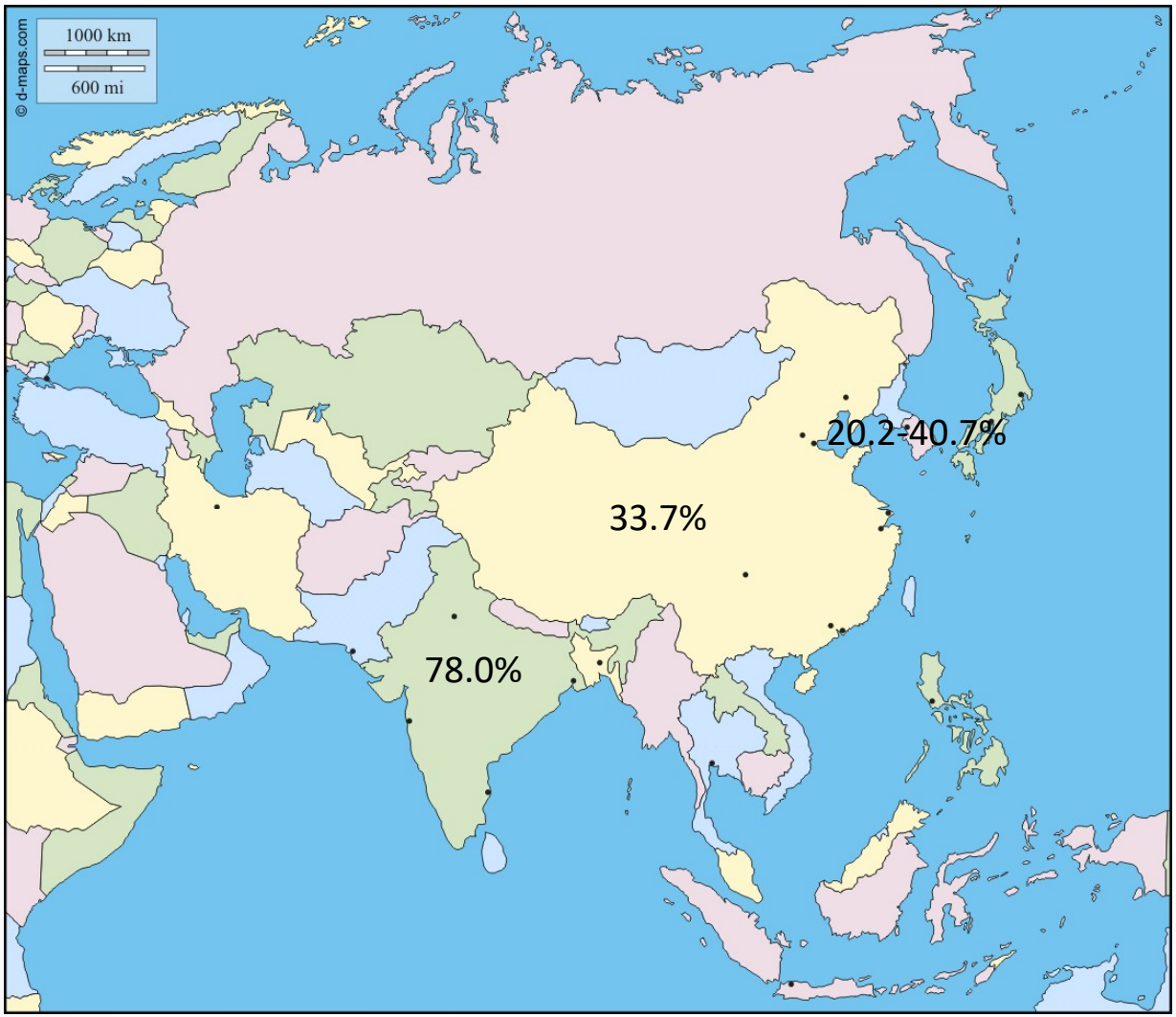
(data from R. Moreau R. et al. Gastroenterology 2013 ; 144 : 1426-1437)



* = Infection-related ACLF

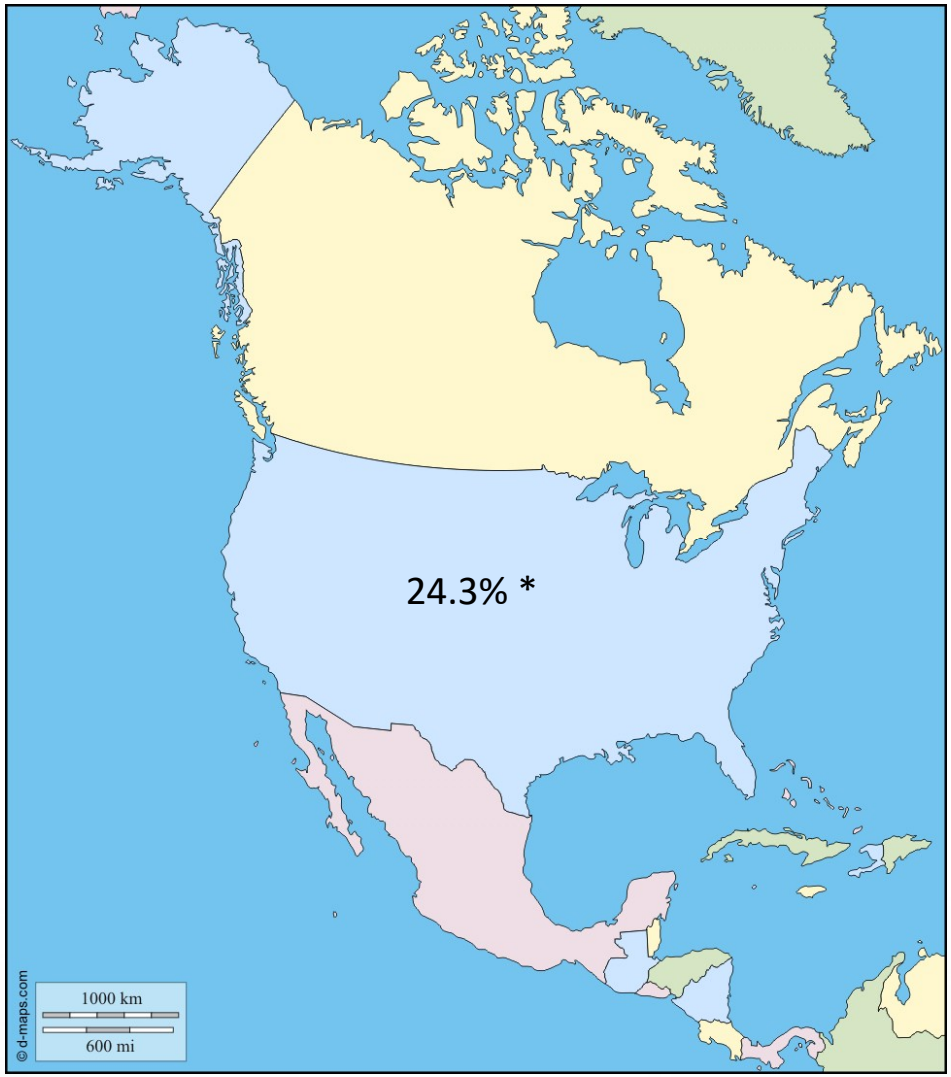
Prevalence of ACLF in Asia

(data from H. Li et al. Sci. Rep. 2016 ; 6 : 25487/D.O.I. 10.1038; TY Kim et al. PlosOne 2016; D.O.I. 10.1371; RK Dhiman et al. WJG 2014 ; 20 : 14934 : 14941; M. Lee. et al. Liver Int. 2015 ; 35 :46-57)



Prevalence of ACLF in North and Central America

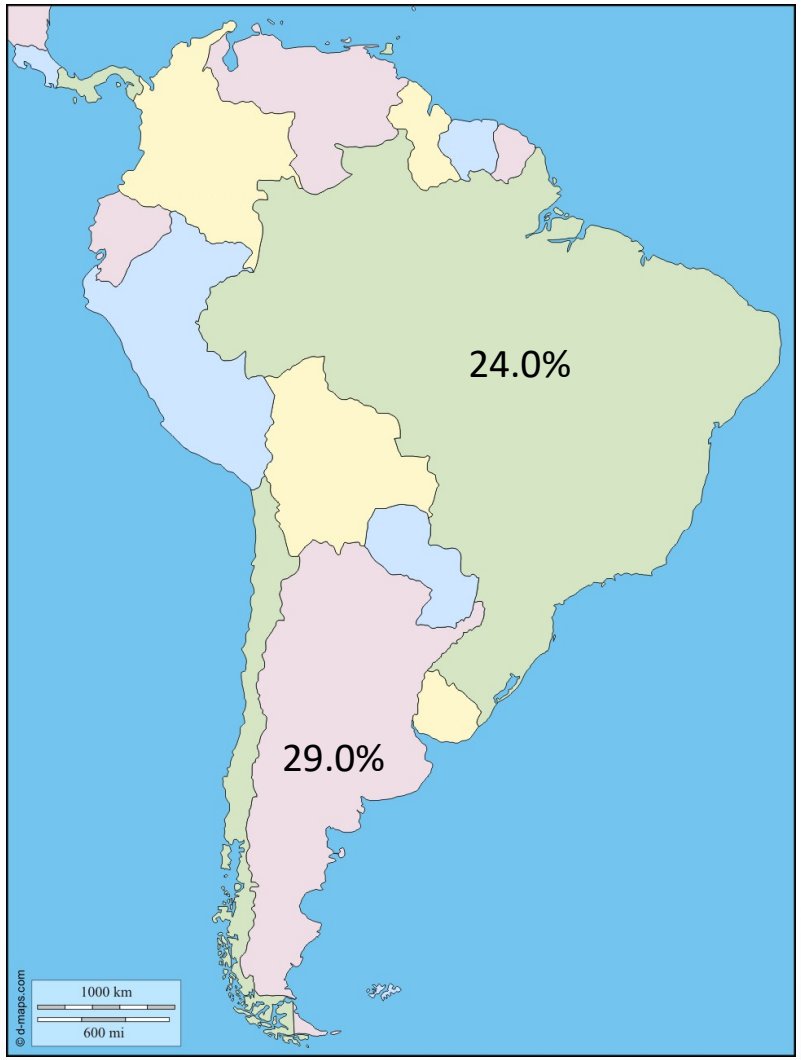
(data from Bajaj JS. et al. Hepatology ; 2014)



* = Infection-related ACLF

Prevalence of ACLF in South America

(data from C. Dominguez et al. WJG 2016 ; 8 : 1529-1534 ; PE Silva et al. Liver Int. 2015 ; 35 : 1516-1523)

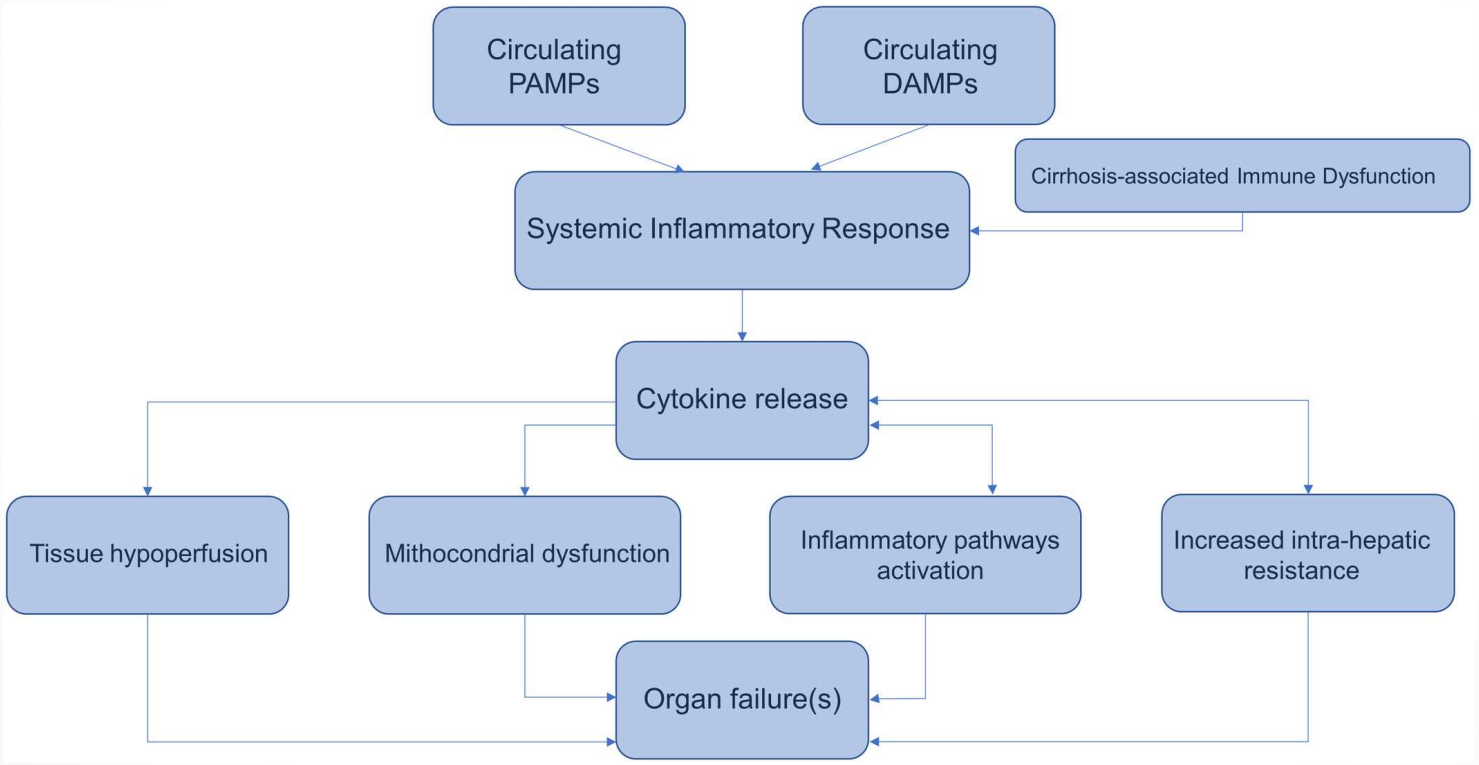


Agenda

- Definition/s of ACLF and epidemiology
- **Pathophysiology**

PATHOPHYSIOLOGY OF ACUTE ON CHRONIC LIVER FAILURE

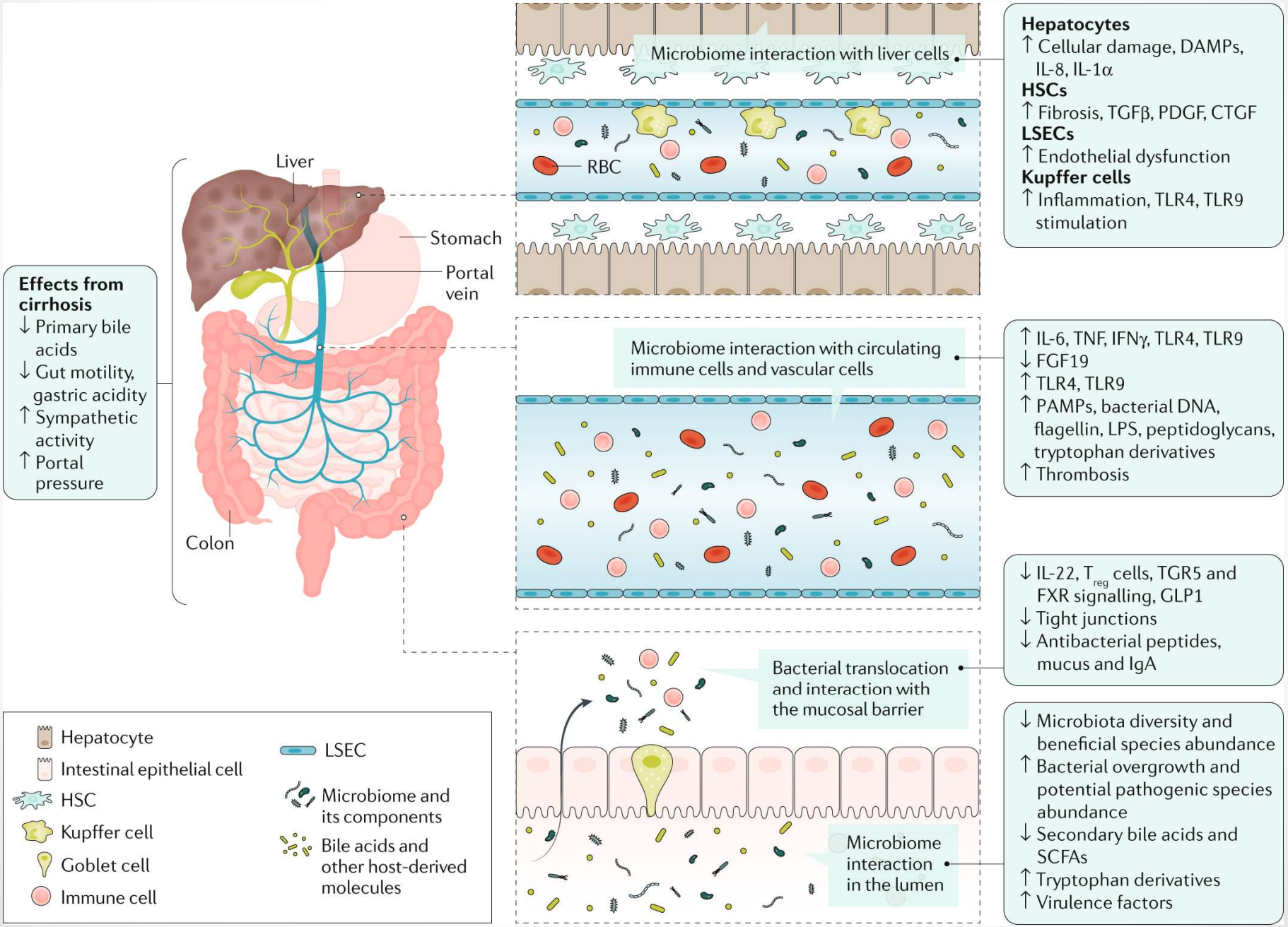
Patients with ACLF showed significantly **higher levels of systemic inflammation** than patients without ACLF. Moreover, in patients with AD who developed ACLF within 28 days from inclusion, markers of inflammation were significantly higher than in patients with AD who did not develop ACLF



the exaggerated systemic inflammatory response in ACLF concerns the exposure to pathogens-associated molecular patterns (PAMPs) and/or damage-associated molecular patterns (DAMPs)

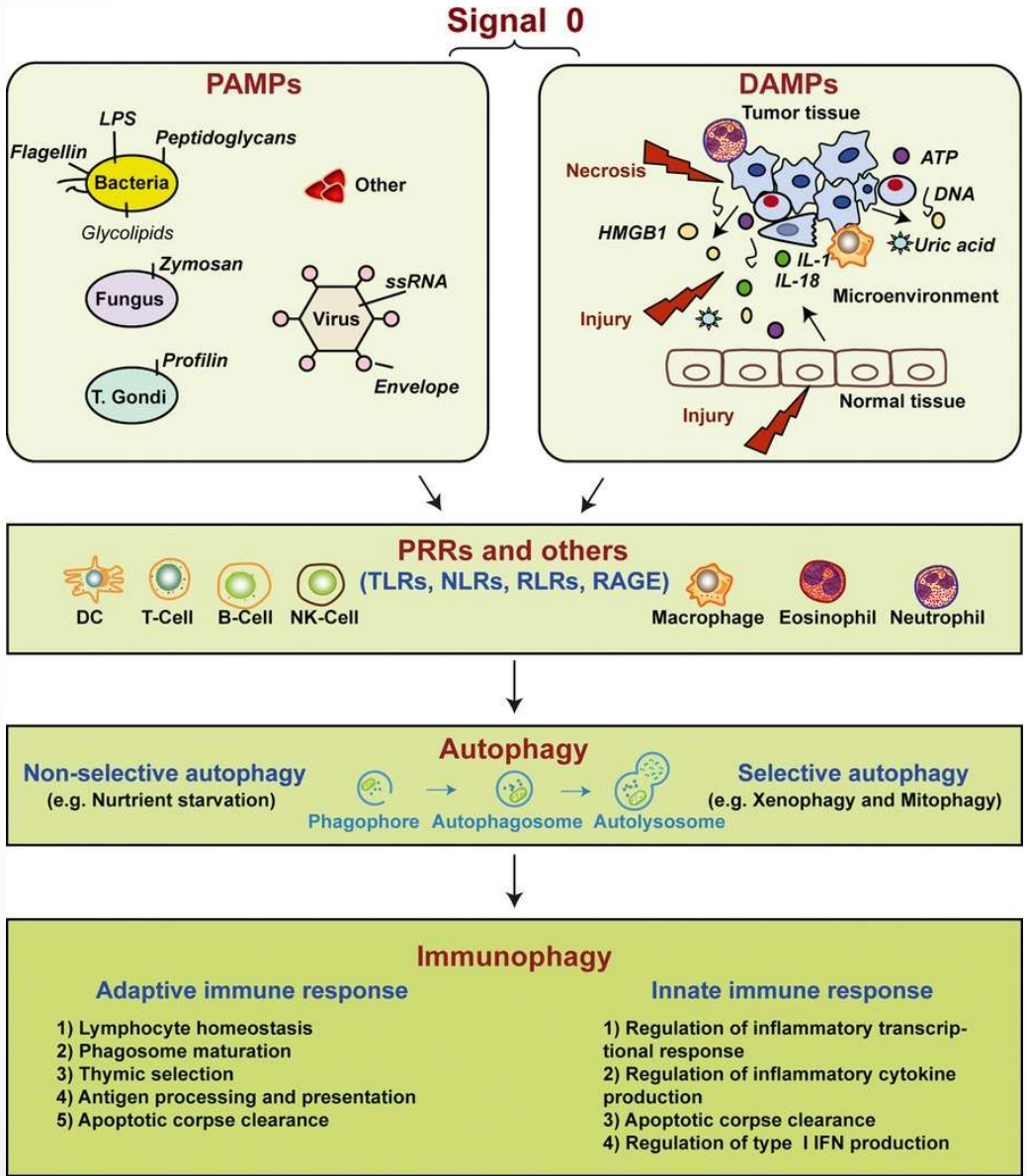
Piano et al Liver International: 16 September 2023

Infections can be favoured by a certain degree of 'cirrhosis-associated immune dysfunction' (CAID), where there is **increased intestinal permeability** and **changes in gut microbiome**



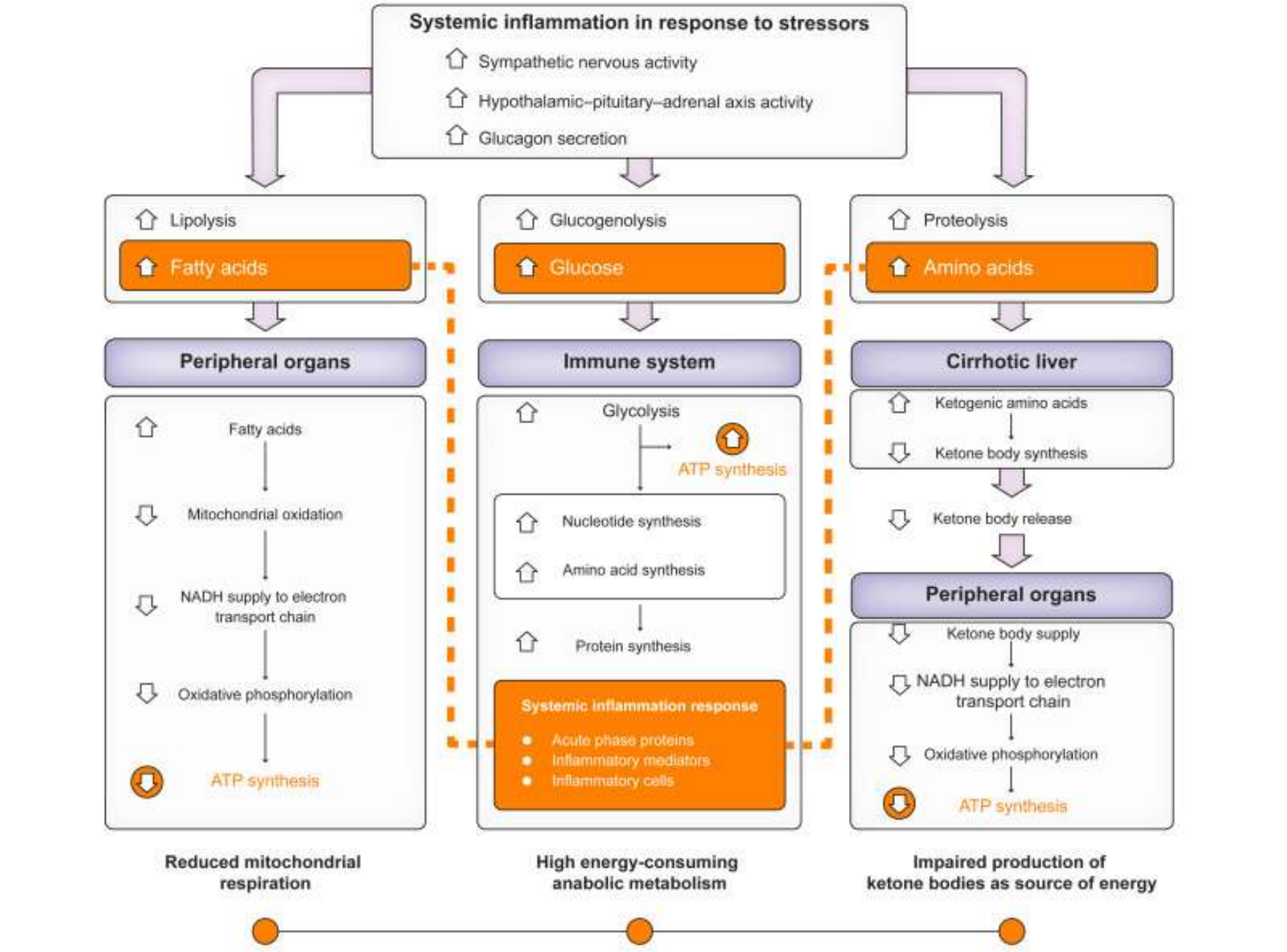
Trebicka et al Gastroenterology & Hepatology 2021

Other mechanisms of inflammation in the absence of bacterial infection/translocation, concern the **release of circulating DAMPs derived from dying or damaged hepatocytes** (such as in the case of alcohol-related hepatitis, HBV flare or other superimposed liver injury) and/or other host cells that bind to and activate specific PRRs



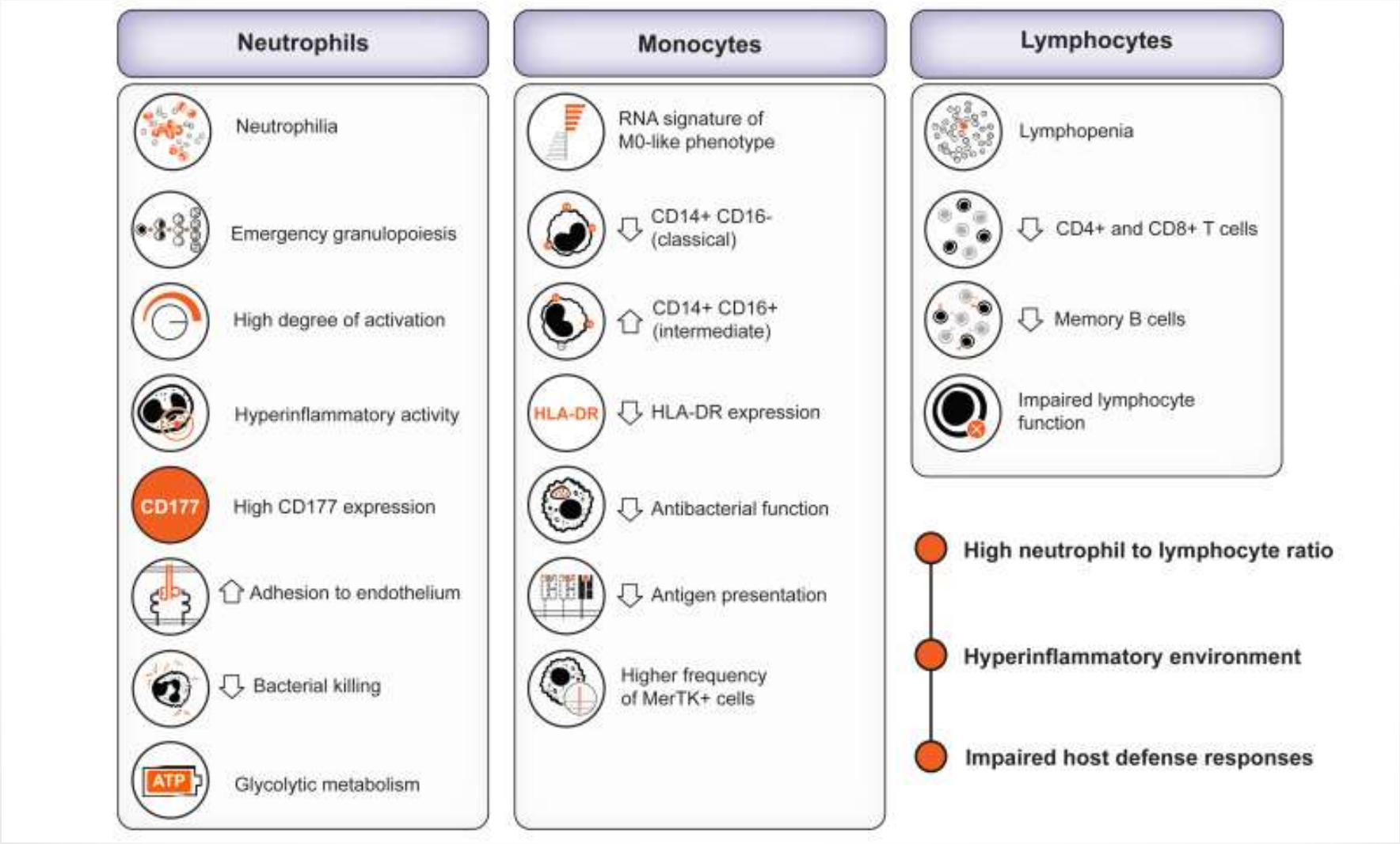
Bianchi et al J Leuk 2007

three major disorders of energetic metabolism in patients with ACLF



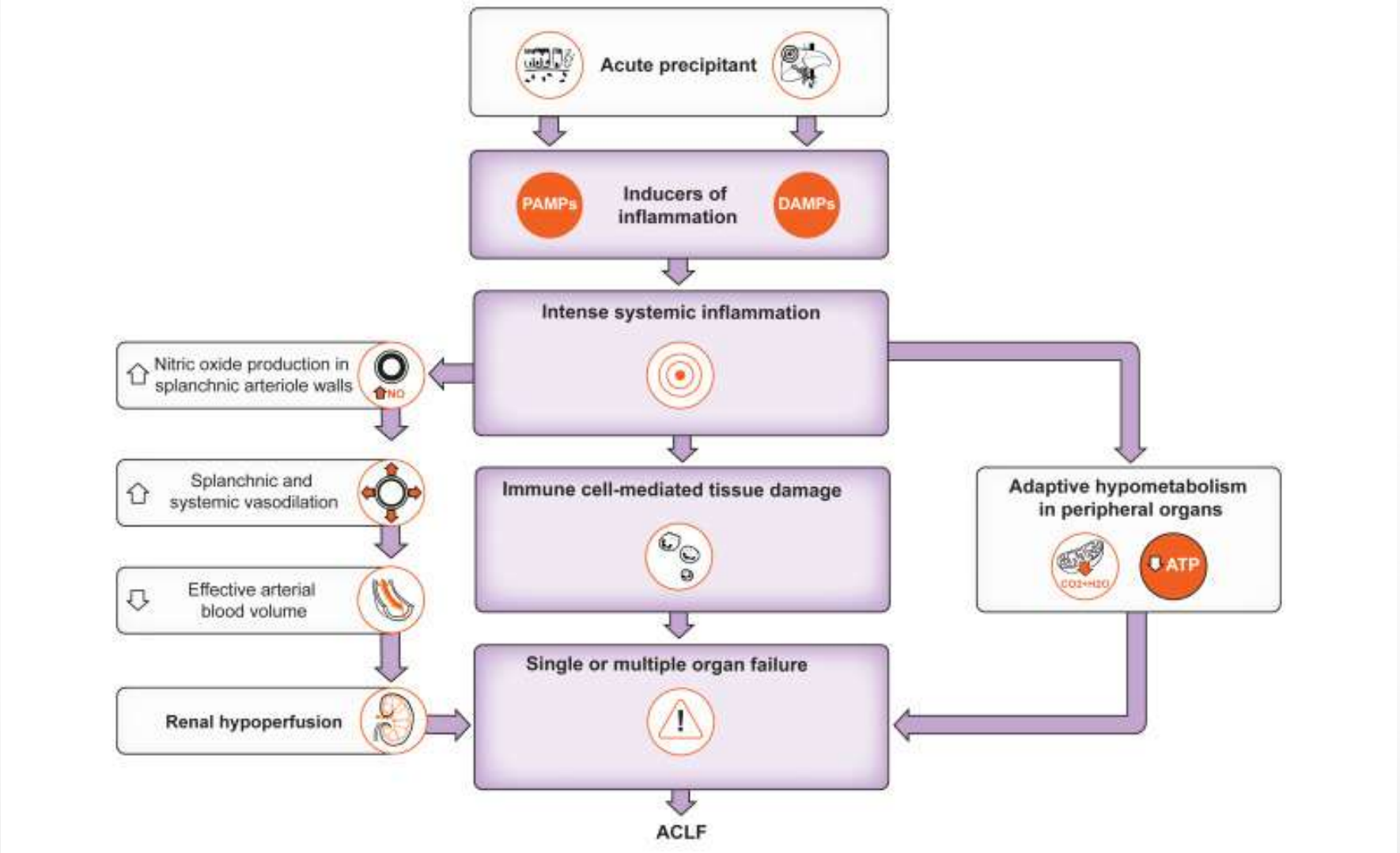
Claria et al J Hepatol June 2023

The immunopathological landscape in peripheral blood of patients with acutely decompensated cirrhosis and ACLF is characterized by neutrophilia and severe lymphopenia



Claria et al J Hepatol June 2023

Hypothesis for organ failure development in ACLF



Claria et al J Hepatol June 2023

The mechanisms by which systemic inflammation induces organ dysfunction and failure involve three different pathways:

- direct damage by immune cells (immunopathology),

- macrovascular/microvascular abnormalities leading to tissue hypoperfusion and competition for nutrients and energy utilization (ATP), needed for inflammatory response with hypometabolism in peripheral organs.

Agenda

- Definition/s of ACLF and epidemiology
- Pathophisiology
- Therapeutic

MEDICAL TREATMENT OF ACUTE ON CHRONIC LIVER FAILURE

Organ Failures management

Circulation

Fluid challenge to mantain MAP≥65 mmHg
Prefer cristalloids when possible
Human albumin in septic shock
Consider vasopressors: norepinephrine as first-line, terlipressin in HRS or as second vasopressor

Brain

Lactulose enemas – Rifaximin
Consider intubation if severe HE

Respiratory

Prefer NIV when possible
Endotracheal intubation if needed to protect airways
Paracentesis to help ventilatory dynamics

Coagulation

Prophylaxis of deep vein thrombosis if not contraindicated
Consider using thromboelatometry to assess need for plasma/platelets/fibrinogen in case of bleeding or invasive procedures

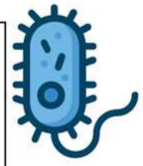
Kidney

Monitor diuresis and renal function
Treat according to the cause (e.g. HRS)
Avoid nephrotoxic drugs
RRT in selected cases as bridge for LT

Precipitant management

Infections

Blood, urine, ascites coltures
Broad spectrum antibiotics ASAP
De-escalation if possible
Consider local epidemiology and resistance
Antifungal therapy only if risk factors



Severe alcoholic hepatitis

Corticosteroids if MDF>32 (e.g. prednisone 40 mg)
Poor response in patients with ACLF and increased risk of infections

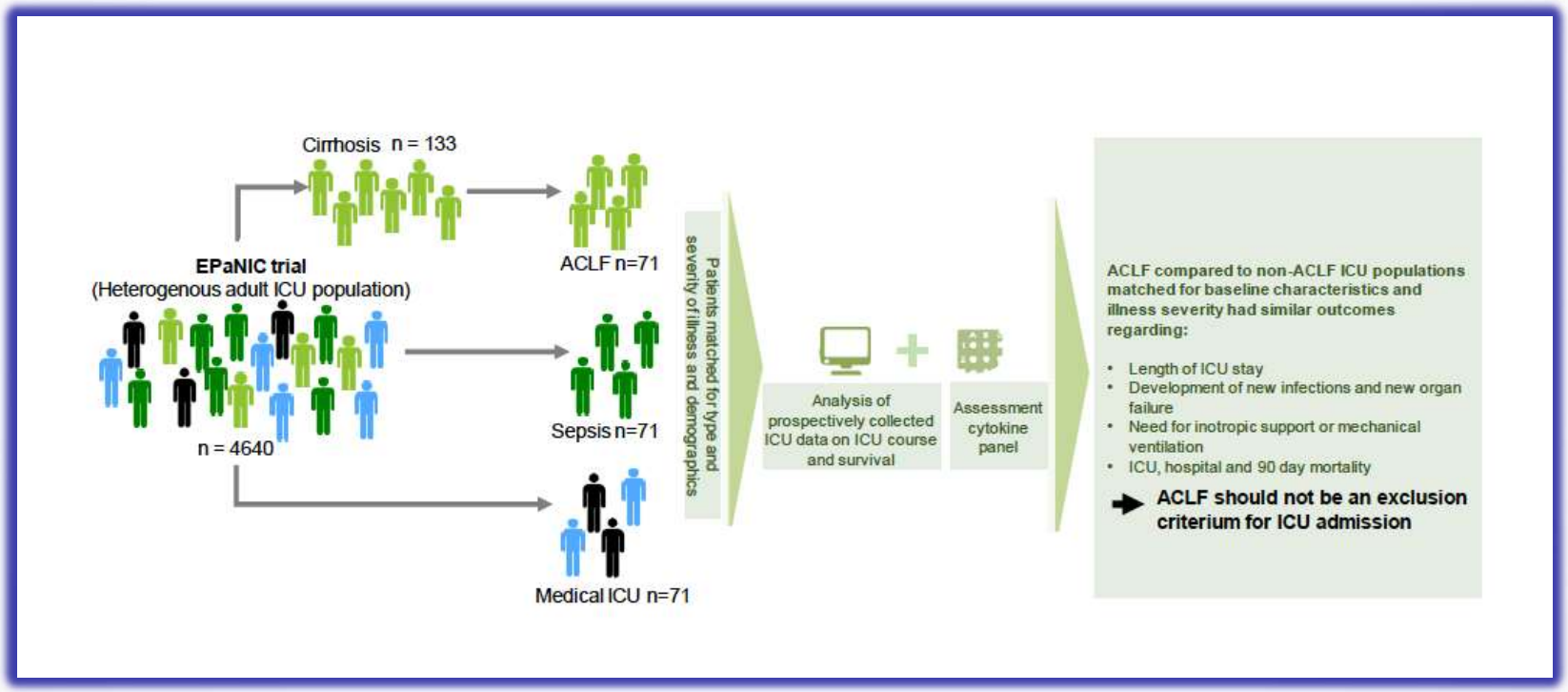
Variceal bleeding

Treat promptly
Consider pre-emptive TIPS
High risk of rebleeding

HBV flare

Use nucleos(t)ide antagonists

Given that ACLF is a serious condition with high short-term mortality, patients with ACLF should be closely monitored and considered for transfer to an intensive care unit (ICU) setting



P. Meersseman et al. J. Hepatol 2018

PREDICT identifies precipitating events associated with the clinical course of acutely decompensated cirrhosis

Jonel Trebicka [1 2 †], Javier Fernandez [1 4 †], Maria Papp [5], Paolo Caraceni [6], Wim Laleman [13], Carmine Gambino [7], Ilaria Giovo [8], Frank Erhard Uschner [2], Christian Jansen [3], Cesar Jimenez [9], Rajeshwar Mookerjee [10], Thierry Gustot [11], Agustin Albillos [12], Rafael Bañares [14], Peter Jarcuska [15], Christian Steib [16], Thomas Reiberger [17], Juan Acevedo [18], Pietro Gatti [19], Debbie L. Shawcross [20]... Osman Cavit Özdogan [84]

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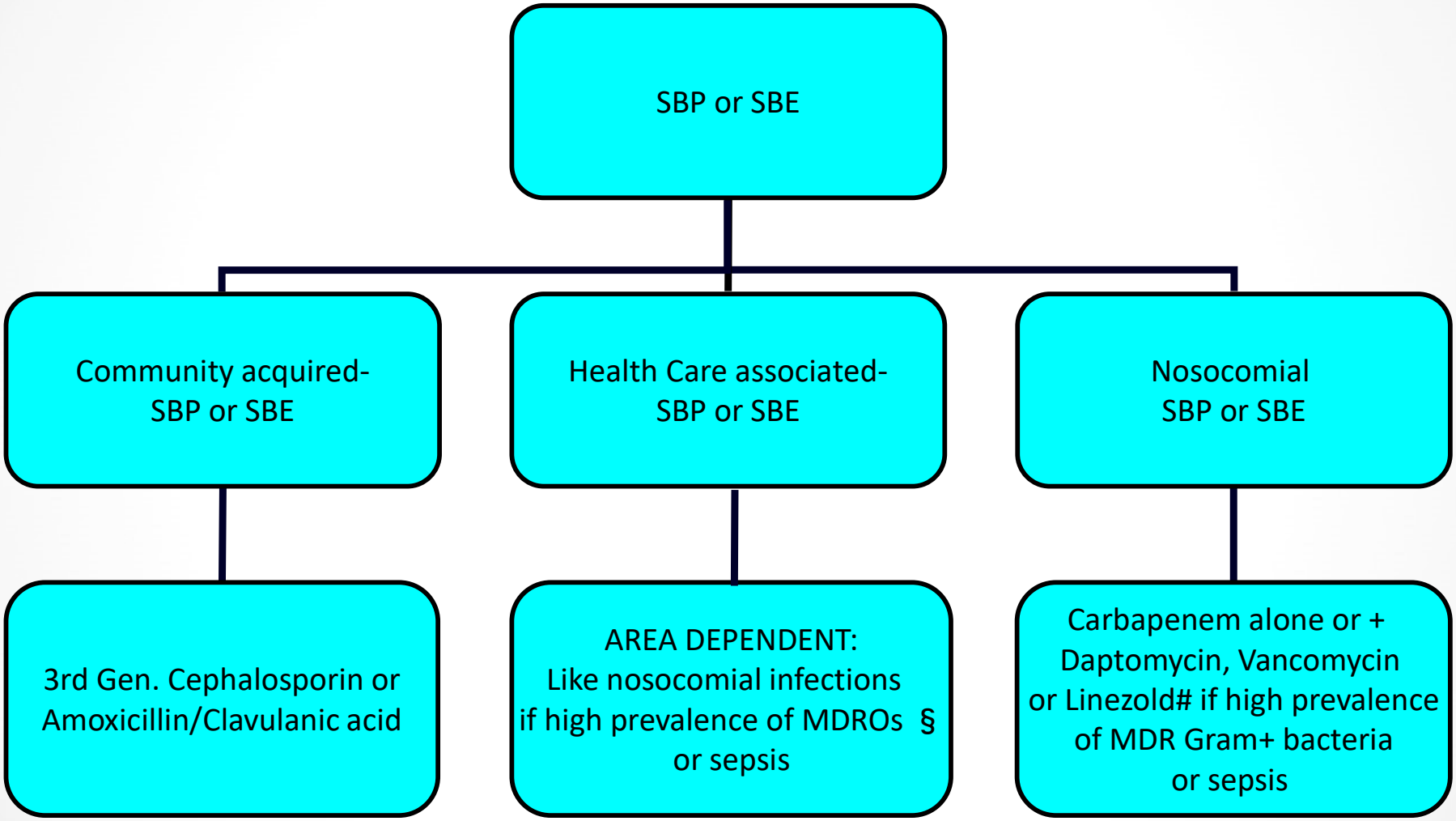
Bacterial infections are the most common precipitant in patients with ACLF, and can frequently complicate the course of ACLF and worsen the prognosis.

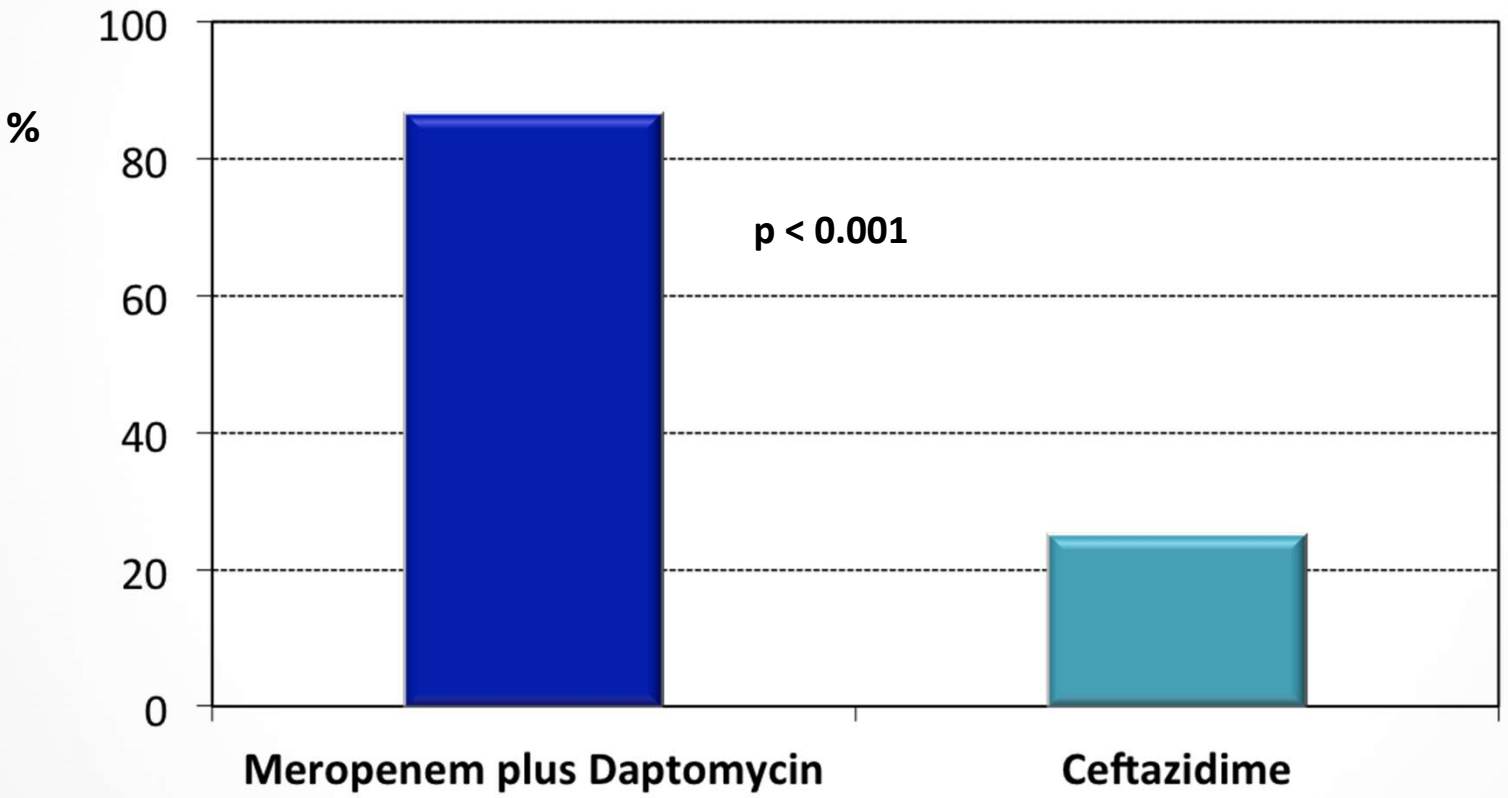
The prevalence of bacterial infection at diagnosis of ACLF is about 50% and among patients with ACLF and no infection at diagnosis, almost 50% develop bacterial infections within 4 weeks.



§ piperacillin/tazobactam in areas with low prevalence of MDROs

***IV vancomycin or teicoplanin in areas with a high prevalence MRSA and vancomycin-susceptible enterococci (VSE). Glycopeptides must be replaced by IV linezolid in areas with a high prevalence of vancomycin-resistant enterococci (VRE).**

Response to first line antibiotic treatment according to the assigned group



S. Piano et al. Hepatology 2016 ; 63 : 1299-309.

Meropenem plus daptomycin for nosocomila SBP

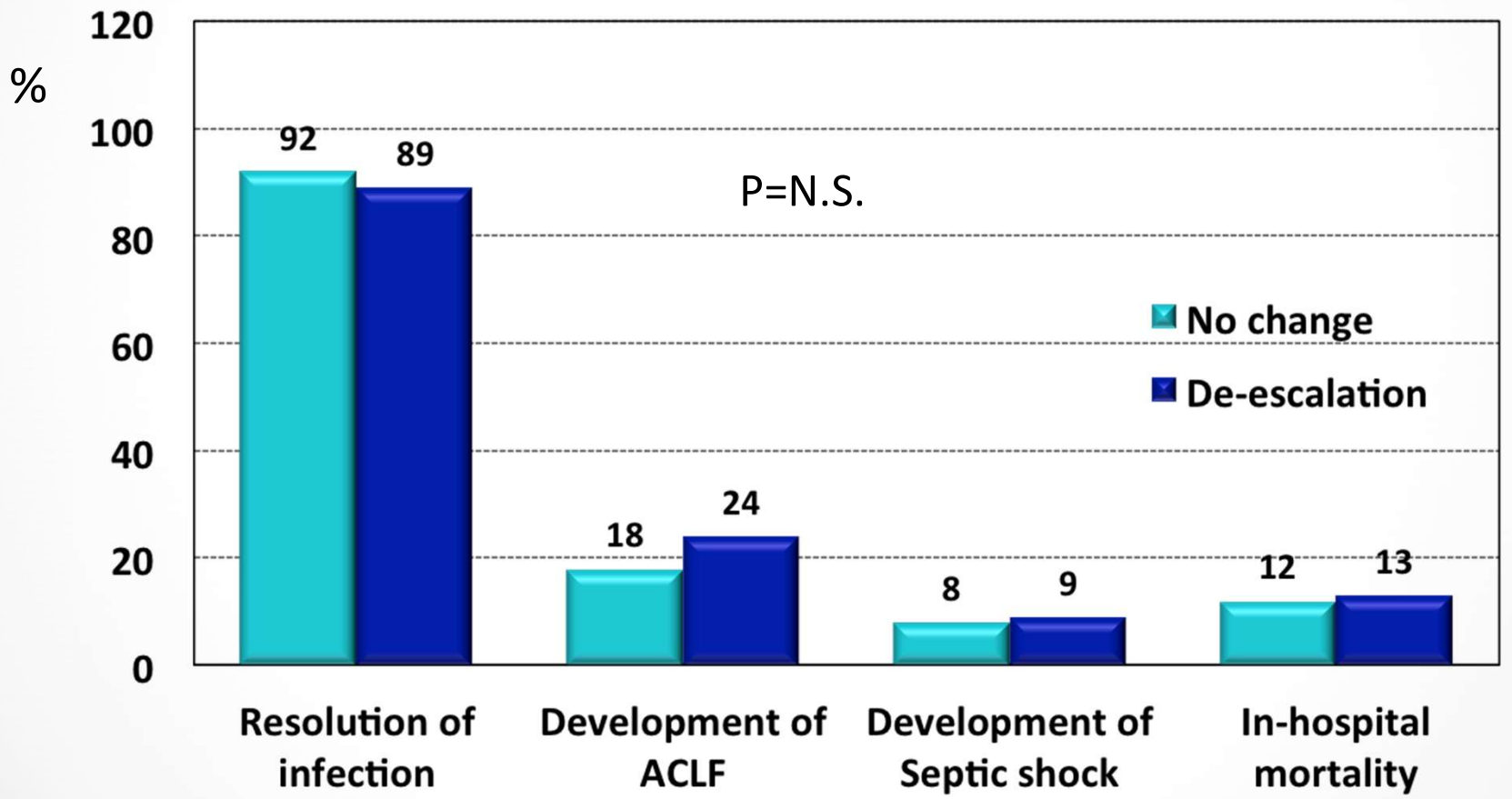
S. Piano et al. Hepatology 2016 ; 63 : 1299-309.

Independent predictors of 90-day survival in patients with ACLF-1 and ACLF-2

Parameter	HR (CI)	P
Appropriate empirical antibiotic tretament	0.41 (0.27-0.62)	< 0.001
Age	1.02 (1.0-1.4)	< 0.05
Bilirubin	1.03 (1.01-1.05)	< 0.01

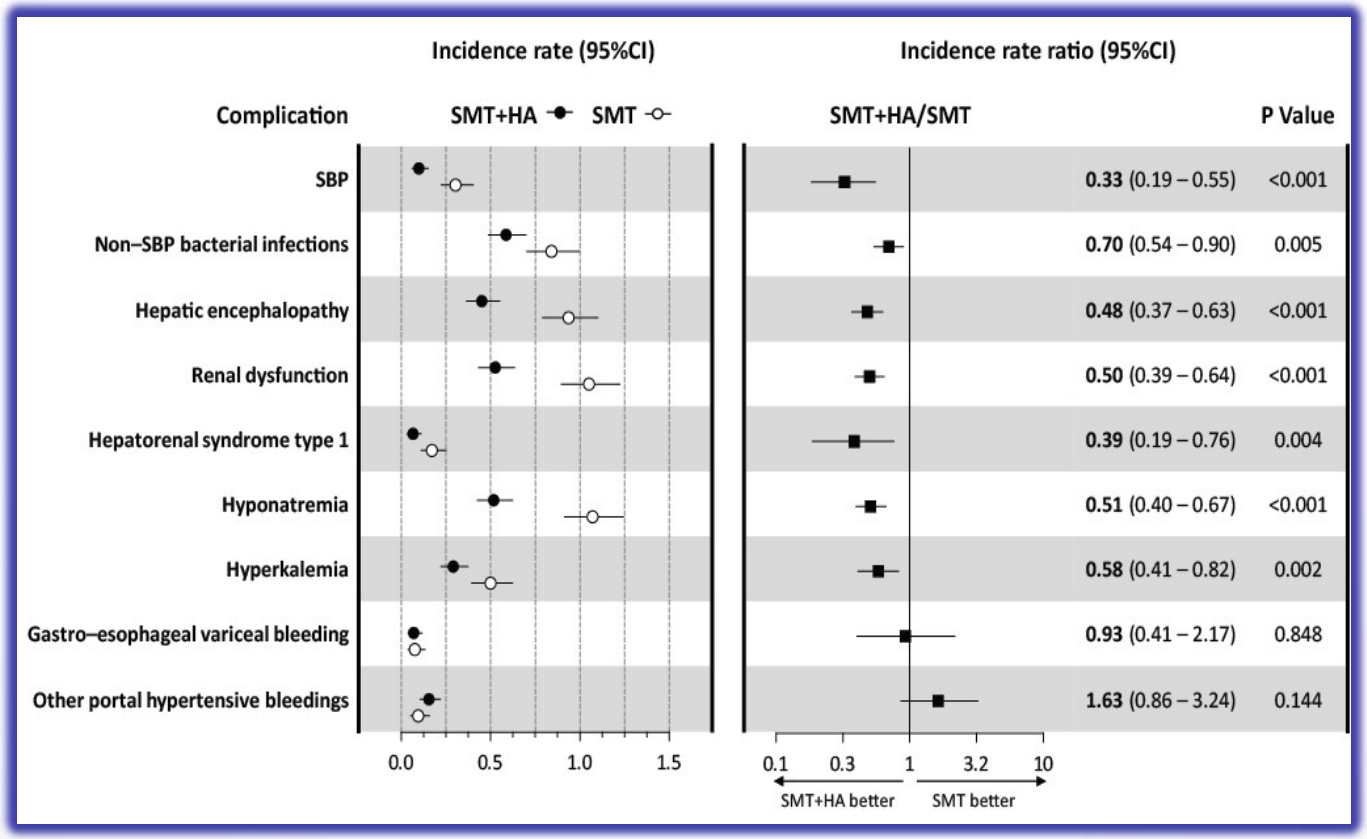
J. Fernandez et al. Gut 2017

Impact of the de-escalation of antibiotic treatment on outcomes



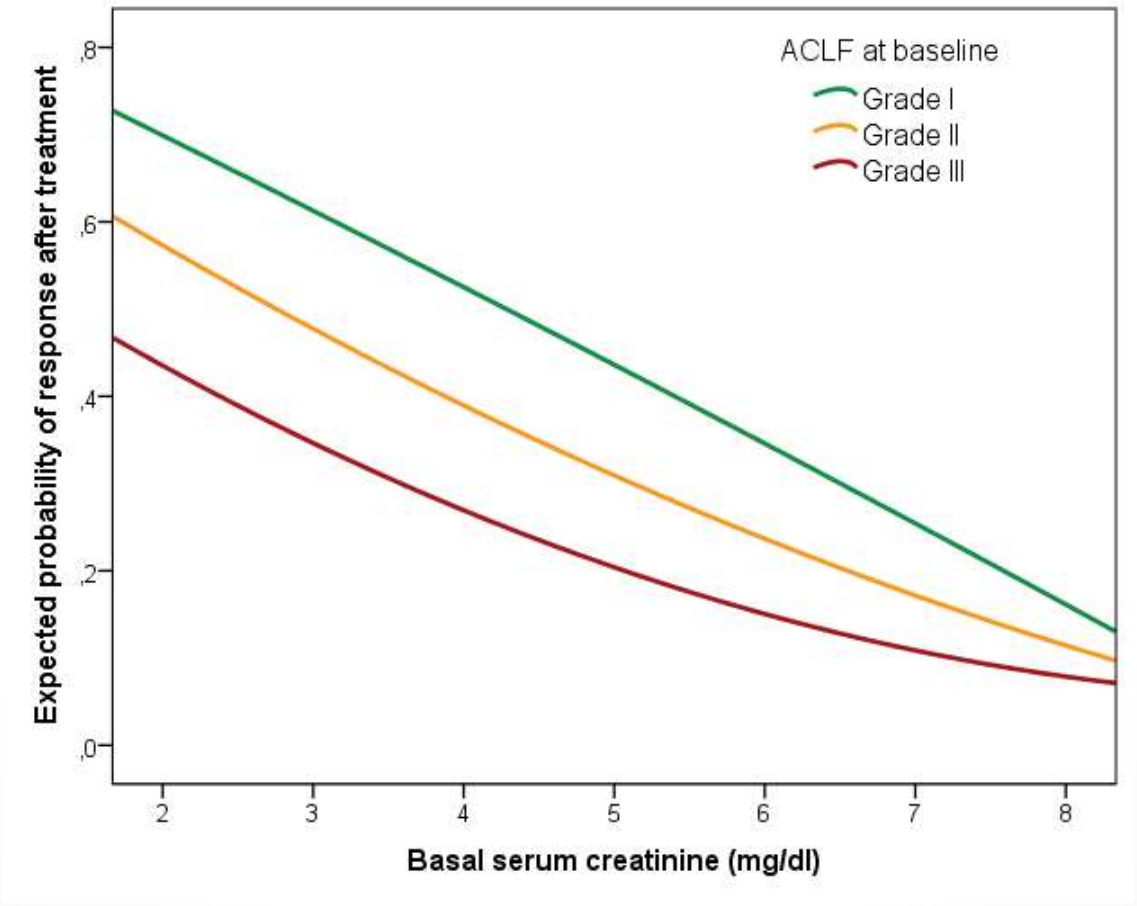
S. Piano et al. ICA Global Study ; EASL The liver Meeting 2018

Impact of long-term i.v. albumin andiministration on complications other than ascites



P. Caraceni et al. ; Lancet ; 2018

Impact of ACLF grade on the rate of response to treatment with terlipressin plus albumin in patients with type 1 HRS



S. Piano et al. Clin. Gastroenterol. Hepatol. 2018

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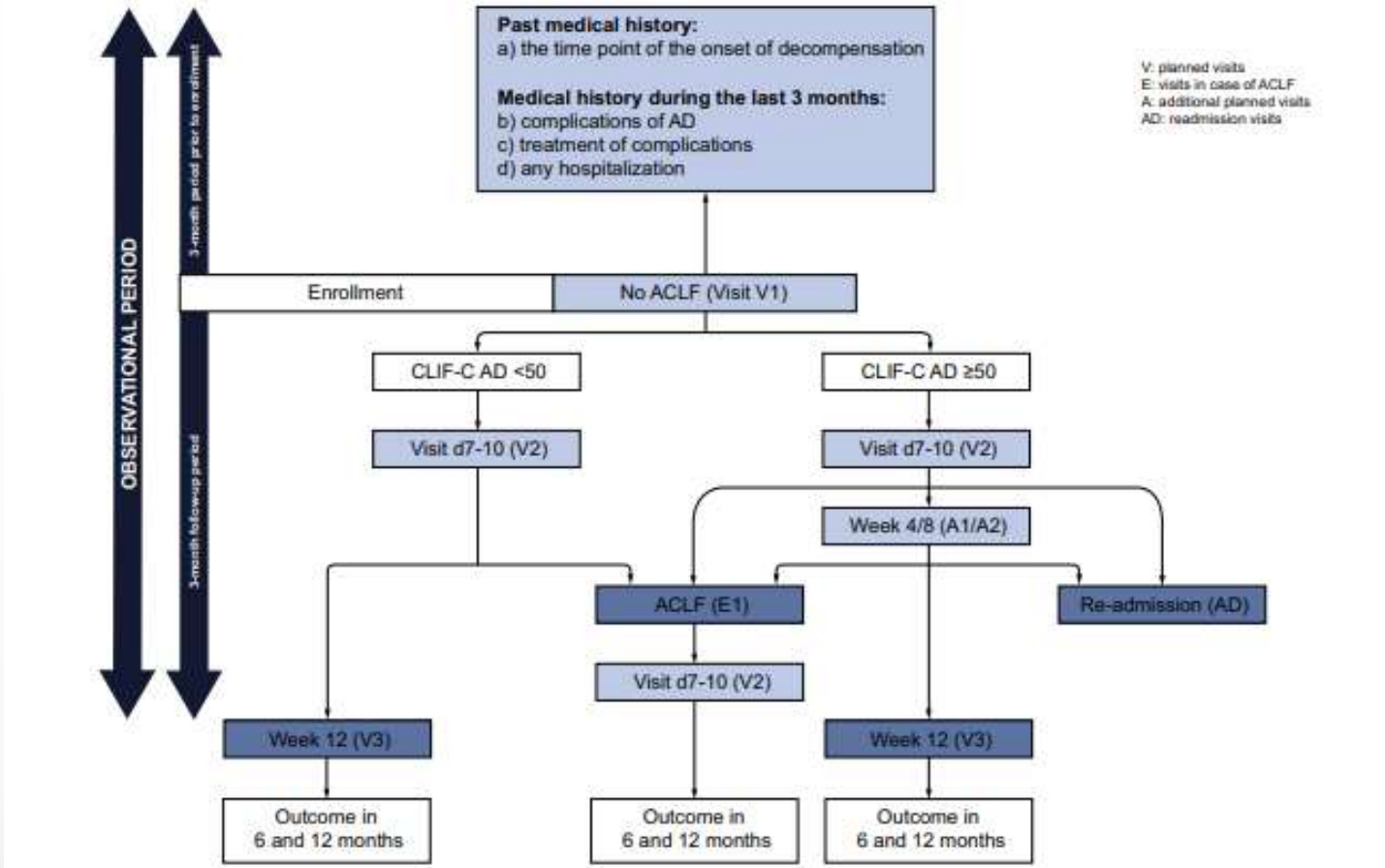
Research Article
Cirrhosis and Liver Failure

JOURNAL OF HEPATOLOGY

The PREDICT study uncovers three clinical courses of acutely decompensated cirrhosis that have distinct pathophysiology☆

Jonel Trebicka[1,2,*], Javier Fernandez[1,4], Maria Papp[5], Paolo Caraceni[6], Wim Laleman[13], Carmine Gambino[7], Ilaria Giovo[8], Frank Erhard Uschner[2], Cesar Jimenez[9], Rajeshwar Mookerjee[10], Thierry Gustot[11], Agustin Albillos[12], Rafael Bañares[14], Martin Janicko[15], Christian Steib[16], Thomas Reiberger[17], Juan Acevedo[18], Pietro Gatti[19], William Bernal[20], Stefan Zeuzem[2], Alexander Zipprich[21], Salvatore Piano[7], Thomas Berg[22],

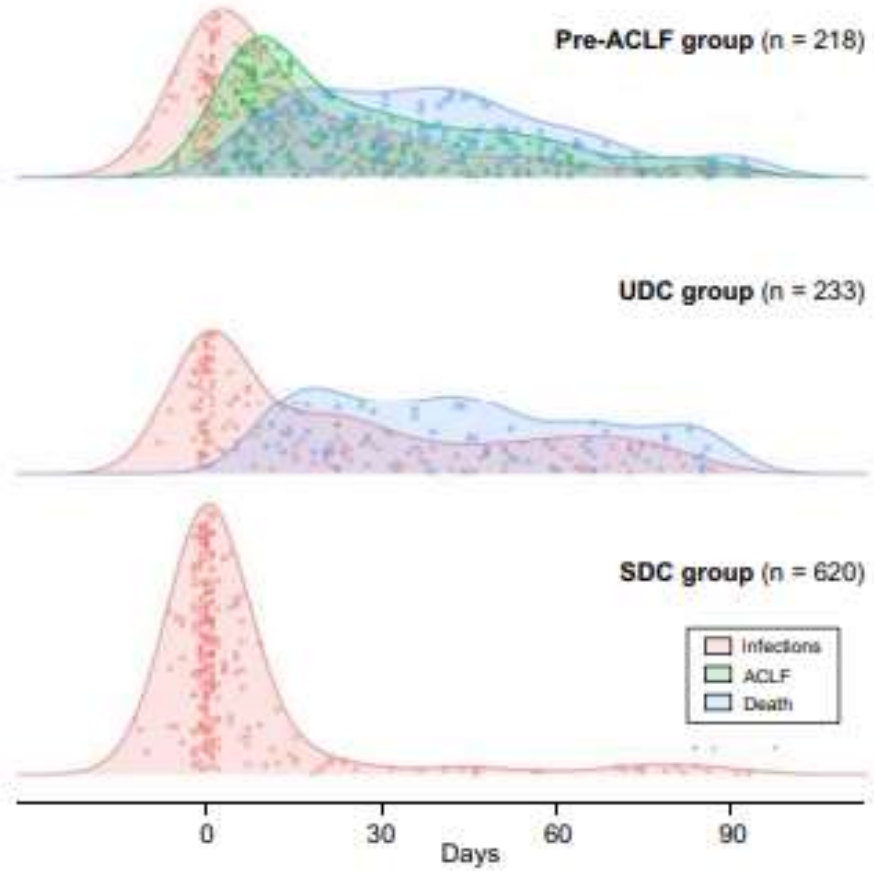


Patients with acutely decompensated cirrhosis without ACLF develop 3 different clinical courses.

- Patients with pre-ACLF develop ACLF within 90 days and have high systemic inflammation and mortality.
- Patients with unstable decompensated cirrhosis suffer from complications of severe portal hypertension.
- Patients with stable decompensated cirrhosis have less frequent complications and lower 1-year mortality risk

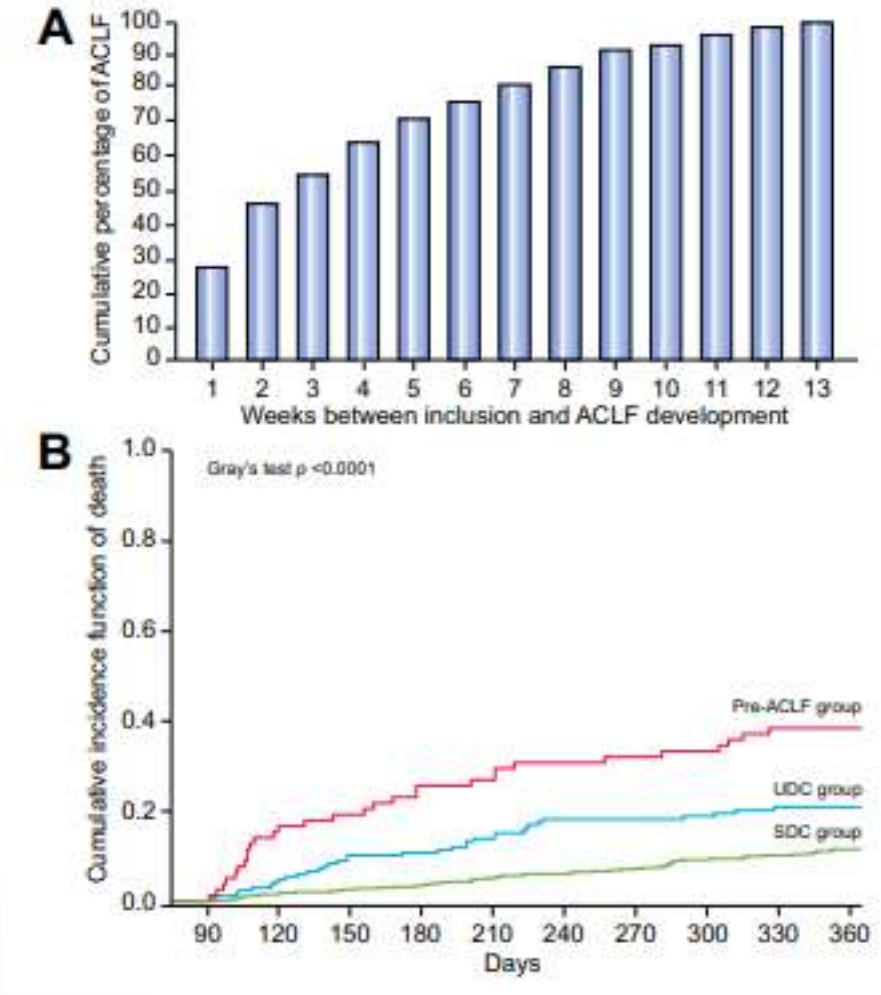
Trebicka et al J Hepatol 2020

Density curves of events during the 3-month follow-up period after enrollment in patients with pre-ACLF, UDC and SDC.



Trebicka et al J Hepatol 2020

Cumulative rates of ACLF and death.

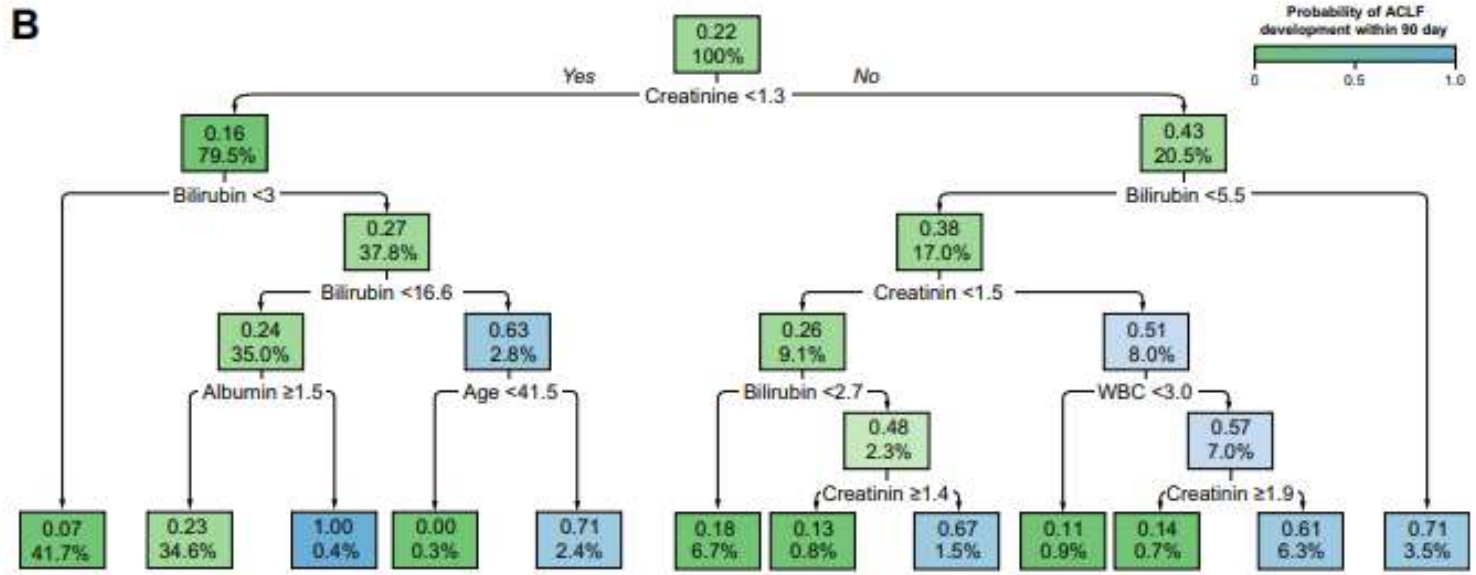


Predictive ability of the CLIF-C ACLF-D score

A

Severity scores	Derivation set (n = 707)	Validation set (n = 364)
	Harrel' C-index (95% confidence interval)	
CLIF-C ACLF-D	0.76 (0.72-0.80)	0.77 (0.72-0.82)
CLIF-C AD	0.70 (0.66-0.74)	0.75 (0.70-0.80)
MELD-sodium	0.70 (0.66-0.74)	0.74 (0.69-0.80)
MELD	0.70 (0.66-0.74)	0.73 (0.67-0.79)
Child-Pugh	0.64 (0.59-0.68)	0.67 (0.60-0.73)

B



Agenda

- Definition/s of ACLF and epidemiology
- Pathophisiology
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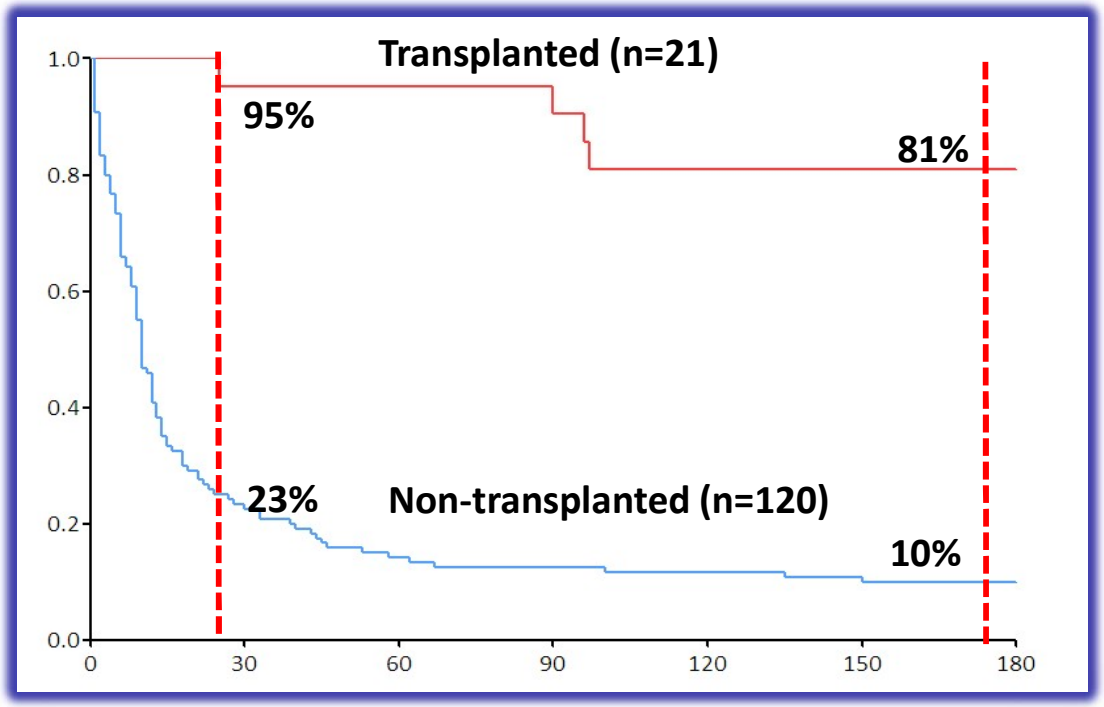
- PRE-ACLF
- **The role of liver transplant in the management of ACLF**

Survival probability after a diagnosis of ACLF grade 2 or 3 in patients receiving or not an early (within 28 days) liver transplant



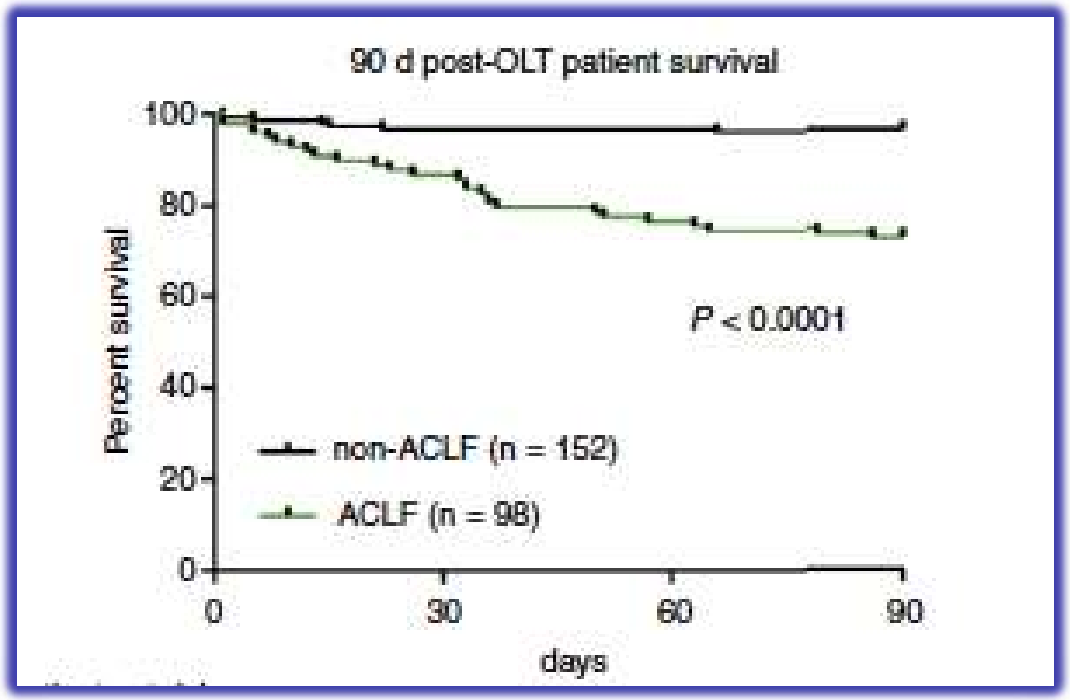
T. Gustot et al. Hepatology 2015; 62 : 243-252

Liver transplant and ACLF

First Author	Experience	Criteria for ACLF	Survival	Notes
T. Gustot (2015)	Canonic study	EASL Clif criteria	80.9 % LT vs 10 % no LT at 6 months after LT	Favors early LT
F. Artu (2017)	Lille/Paris/ Montpellier	EASL Clif criteria	83.9 % LT vs 7.9 % no LT at 1 year	Favors early LT; patients with ACLF have high complication rate
KR. Reddy (2015)	NACSELD	NACSELD criteria	95 % LT vs < 10 % no LT at 6 months	Favors LT
A. Finenstedt (2013)	Innsbruck	APASL criteria	Same 5 year survival (82%) after LT with or without ACLF	Favors LT
E. Levesque (2017)	Creteil	EASL Clif	79.3 vs 96.2 % at 3 months after LT with or without ACLF	Does not favor LT

Adapted from JS. Bajaj et al. Hepatology 2018; 62 : 243-252

Survival probability in patients receiving liver transplant according to the presence of ACLF



P. Huebener et al. Aliment. Pharmacol. Ther. 2018 ; 47 : 1502-1510

Potentially inappropriate LT

Do all organ failures have the same potential impact on early mortality after transplantation?

M. Linecker et al. J. Hepatol. 2017

Organ failure/s in patients who underwent LT and in those who died/delisted

Type of organ failure	Transplanted (n° = 47)	Delisted/Dead (n° = 57)	*P*
Rspiratory failure, n°	17	41	< 0.001
Circulatory failure, n°	16	42	< 0.001
Renal failure, n°	37	43	N.S.
Cerebral failure, n°	55	79	< 0.005

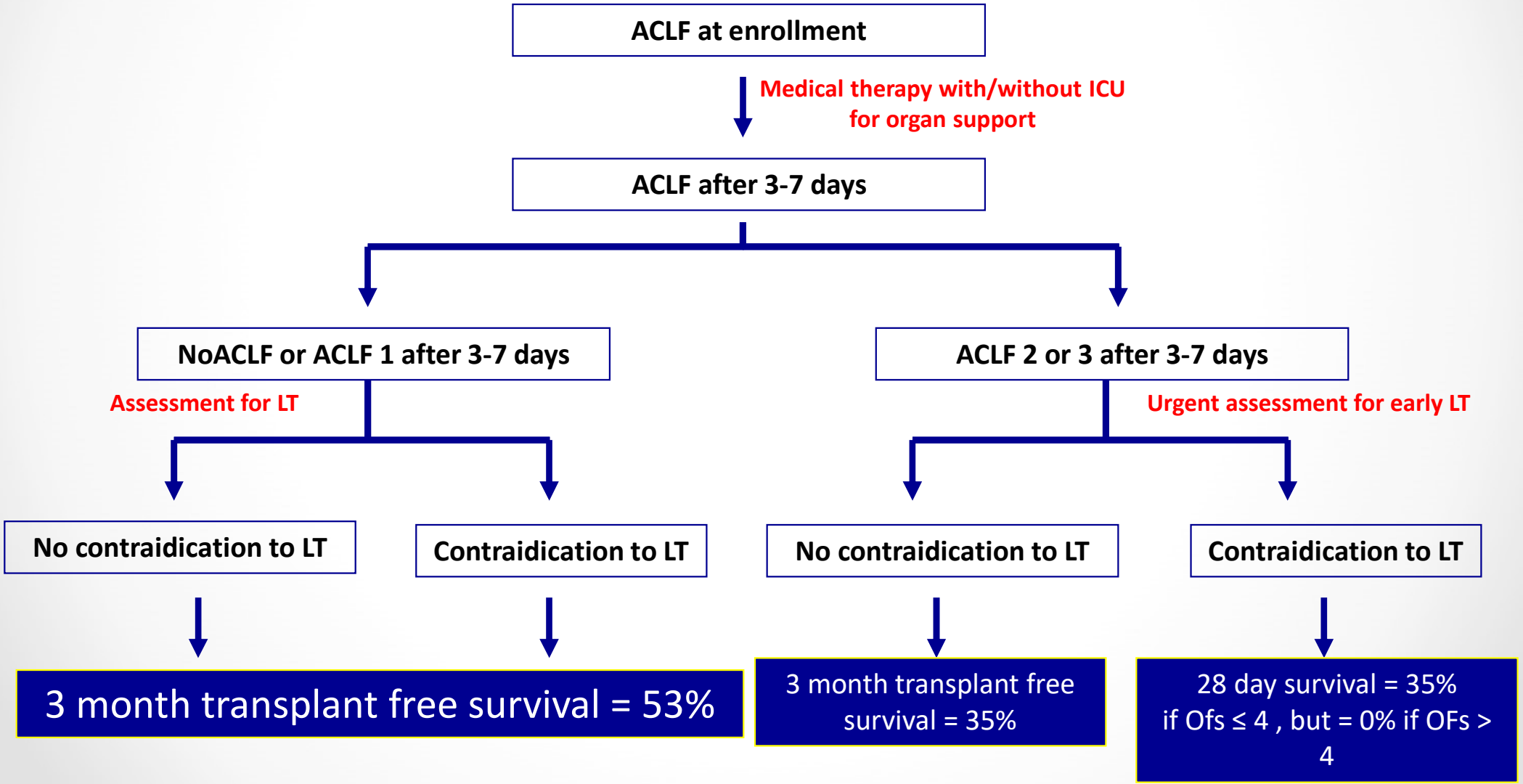
Adapted from KR. Reddy et al. Liver Transpl. 2015 ; 21 : 881-888.

Proposed absolute and relative pre-LT conditions that can define an inappropriate LT

Absolute	Relative
	Increased ventilation support ($FIO_2 \geq 0.5$)
Circulatory failure requiring 2 vasopressors	Intestinal ischemia
Severe respiratory failure requiring maximal ventilation support (FiO2 ≥ 0.8, high PEEP) or on ECMO	Severe frailty/sarcopenia
Brain edema plus erniation or no cerebral circulation	Aggregation of severe chronic comorbidities
Severe pulmonary hypertension mPAP > 50 mmHg mPAP 35-50 mmHg with elevated PVR	
Ongoing infections with the following featires: spetic bacteraemia/fungaemia, septic shock, fungal or bacterial SPB, tissue invasive fungal infection	
Ongoing severe/necrotising pancreatitis	
Aggragation of several relative conditions	

Adapted from M. Linecker et al. J. Hepatol. 2017; (Epub ahead of print)

Proposed algorithm for the management of ACLF



T. Gustot et al. Hepatology 2015; 62 : 243-252

Summary

- ACLF is a syndrome quite common in patients with chronic liver disease, particularly but not exclusively in those with cirrhosis.
- In Western countries but also in some Asian countries ACLF (India, Korea) ACLF is very often precipitated by bacterial infections, particularly when sustained bt MDR or XDR bacteria, and by active alcoholism.
- In some other Asian countries (China) hepatic insults (i.e. flare of hepatitis B or E) are the commonest precipitating factor of ACLF.
- The type of precipitating factor may change the phenotype and the evolution of ACLF.
- Prognosis is dependent upon the grade of ACLF at diagnosis and on its evolution during the first 3-6 days.
- Bacterial infections either on diagnosis or during the follow up have a deep, relevant impact on 90-day survival.
- Therapeutic measures are limited but should be apllied appriopriately.
- Emergent liver transplanation should be considered in patients with ACLF grade 2 or 3 after 3-7 days after the onset of the syndrome.