INDESYS Hepatology Club

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Acute-on-Chronic Liver Failure

Terminology, Epidemiology, Pathophysiology, Management

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Outline

- Terminology
- Epidemiology
- Pathophysiology
- Management
- Research agenda

Consortia Which Developed ACLF Definitions

- EASL-Chronic Liver Failure (CLIF) Consortium
- North American Consortium for the Study of End-Stage Liver Disease (NACSELD)
- APASL ACLF Research Consortium (AARC)

Defining Some Terms

- Acutely decompensated cirrhosis = recent ascites, HE, GI hemorrhage, or any combination of these disorders in patients with cirrhosis

- Clinically apparent precipitant of acute decompensation:
  - Extrahepatic: acute infection, GI hemorrhage
  - Intrahepatic: alcohol-related hepatitis
  - See EASL CPG

- Sort-term mortality rate = % of patients who died within 28 days after enrollment, without having received LTx

Moreau et al. Gastroenterology 2013;144:1426-37.e1-9. EASL CPG. J Hepatol 2023;79:461-91.

EASL-CLIF Conducted the CANONIC Study

- Prospective, European, agnostic, observational study designed to determine criteria for ACLF in patients nonelectively admitted for acutely decompensated cirrhosis
  - With or without prior decompensation
  - With or without ongoing clinically apparent precipitant(s)
- Prespecified:
  - Criteria of organ failure (OF) for each of 6 major organ systems
  - ACLF should be associated with short-term mortality rate ≥15%
- Data collected on granular eCRF; continuous monitoring by skilled data managers
- 1,343 patients enrolled in 2011; analyzed in 2011-12.

Moreau et al. Gastroenterology 2013;144:1426-37.e1-9.

The CLIF-C OF Scoring System

Organ System	1 Point	2 Points	3 Points
Liver	Bilirubin <6 mg/dl	Bilirubin 6.0–11.9 mg/dl	Bilirubin ≥12 mg/dl
Kidney	Creatinine <1.5 mg/dl Creatinine 1.5–1.9 mg/dl	Creatinine 2.0–3.4 mg/dl	Creatinine ≥3.5 mg/dl or RRT
Brain (West Haven criteria)	Grade 0	Grade 1–2	Grade 3–4
Coagulation	INR <2.0	INR 2.0–2.4	INR ≥2.5
Circulation	MAP ≥70 mm Hg	MAP <70 mm Hg	Vasopressor requirement
Respiration	Pao_2/Fio_2 >300 Spo_2/Fio_2 >357	Pao_2/Fio_2 201–300 Spo_2/Fio_2 215–357	Pao_2/Fio_2 ≤200 Spo_2/Fio_2 ≤214

Jalan, Saliba, Pavesi, et al. J Hepatol 2014;61:1038-47. EASL CPG. J Hepatol 2023;79:461-91.

EASL-CLIF Definition of ACLF

Patient Group	Prevalence	Short-Term Mortality	Assigned Grade
	% of patients		
Absence of OF	68	4.5	Absence of ACLF
Single, nonkidney OF without KD or BD	10	6	
Single KF	7	19	ACLF-1
Single, nonkidney OF with KD or BD	4	28	ACLF-1
Two OFs	7.5	32	ACLF-2
Three OFs	2	68	ACLF-3
Four to 6 OFs	1.5	89	ACLF-3

Moreau et al. Gastroenterology 2013;144:1426-37.e1-9.

Markers of Organ Function Associated with Short-Term Mortality in ACLARA (Multivariable Analysis)

Variable at Enrollment	Subdistribution Hazard Ratio (95% CI)
MAP, in 1-mm Hg units	0.99 (0.97 to 1.00)
SpO_2/FiO_2, in 1 units	0.96 (0.95 to 0.98)
Albumin, in 1-g/dl units	0.68 (0.53 to 0.86)
Creatinine, in 1-mg/dl units	1.20 (1.11 to 1.30)
INR, in 1 units	1.41 (1.24 to 1.60)

Farias, Curto Vilalta et al. Gastroenterology 2023;165:696-716.

Database Used by NACSELD

- Data prospectively collected on a REDCap (Research Electronic Data Capture) tool
  - From 2,675 patients
  - Nonelectively admitted for acutely decompensated cirrhosis, with or without prior decompensation
  - With or without ongoing clinically apparent extra- or intra-hepatic precipitant(s)
- Prespecified:
  - OF criteria for each of 4 organ systems (kidney, brain, circulation, respiration)
  - Liver failure, coagulation failure were not considered.

Bajaj et al. Hepatology 2014;60:250-6.
O'Leary et al. Hepatology 2018;67:2367-74.

OF Diagnosis by NACSELD

- **Kidney: Need for RRT**
- **Brain: HE grade 3 or 4 (West Haven)**
- **Circulation: shock refractory to fluid resuscitation requiring vasopressors**
- **Respiration: Need for bilevel positive airway pressure or mechanical ventilation**

NACSELD focus: severe ICU patients

Bajaj et al. Hepatology 2014;60:250-6. O'Leary et al. Hepatology 2018;67:2367-74.

ACLF Definition by NACSELD

Number of OFs	Probability of Dying by 30 Days
0	4%
1	12%
2	29%
3	54%
4	77%

Bajaj et al. Hepatology 2014;60:250-256.

ACLF when ≥2 OFs

‘Liver-Centric’ APASL Definition of ACLF

- Based on opinion of APASL experts who analyzed a database
  - Data collection (eCRF?) & management: opaque
- Includes: patients with compensated cirrhosis or non-cirrhotic CLD, who had a first episode of acute liver deterioration due to an acute insult directed to the liver
- Defines ACLF as “acute hepatic insult manifesting as jaundice (bilirubin ≥5 mg/dl) and coagulopathy (INR ≥1.5) complicated within 4 weeks by clinical ascites, HE, or both”
- Excludes: Extrahepatic precipitants; OFs involving kidney, respiration, circulation.

Sarin et al. Hepatol Int 2009;3:269-82. Hepatol Int 2014;8:453-71. Hepatol Int 2019;13:353-90.

Key Takeaways

- For patients hospitalized with acutely decompensated cirrhosis, the EASL-CLIF definition of ACLF should be used (evidence-based definition, considers the function of 6 major organ systems, covers a large spectrum of severity).

- The NACSELD definition of ACLF mainly applies to ICU patients with acutely decompensated cirrhosis.

- The APASL definition applies to patients who are different from those considered in EASL-CLIF and NACELD definitions.

Can we Reconcile the Definitions?

- Kulkarni & Sarin hypothesis:
  - APASL-ACLF: Early stages
  - EASL-CLIF ACLF: Intermediate stages
  - NACSELD ACLF: Late stages
- Large international prospective longitudinal studies are needed.

Kulkarni & Sarin.J Hepatol. 2024 Aug;81:360-66.

Outline

- Epidemiology

Global Burden of ACLF

- Meta-analysis of 30 cohorts using EASL-CLIF criteria; ~190,000 patients hospitalized for decompensated cirrhosis
- 5 in 10 patients had alcohol-related cirrhosis; 3 in 10 patients had viral cause
- 4 in 10 patients had ACLF
- 6 in 10 patients with ACLF died by 90 days vs. 1 in 10 patients without ACLF

Mezzano et al. Gut 2022;71:148-55.

Global Burden of ACLF

- Meta-analysis of 30 cohorts using EASL-CLIF criteria; patients hospitalized for decompensated

- This study shows that the global burden of ACLF is high.
- However, it used both prospective and retrospective studies; no information on MASLD & new Rx.
- Large national & international, granular, prospective epidemiological studies are needed.

10 patients without ACLF

Mezzano et al. Gut 2022;71:148-55.

Outline

- **Pathophysiology**

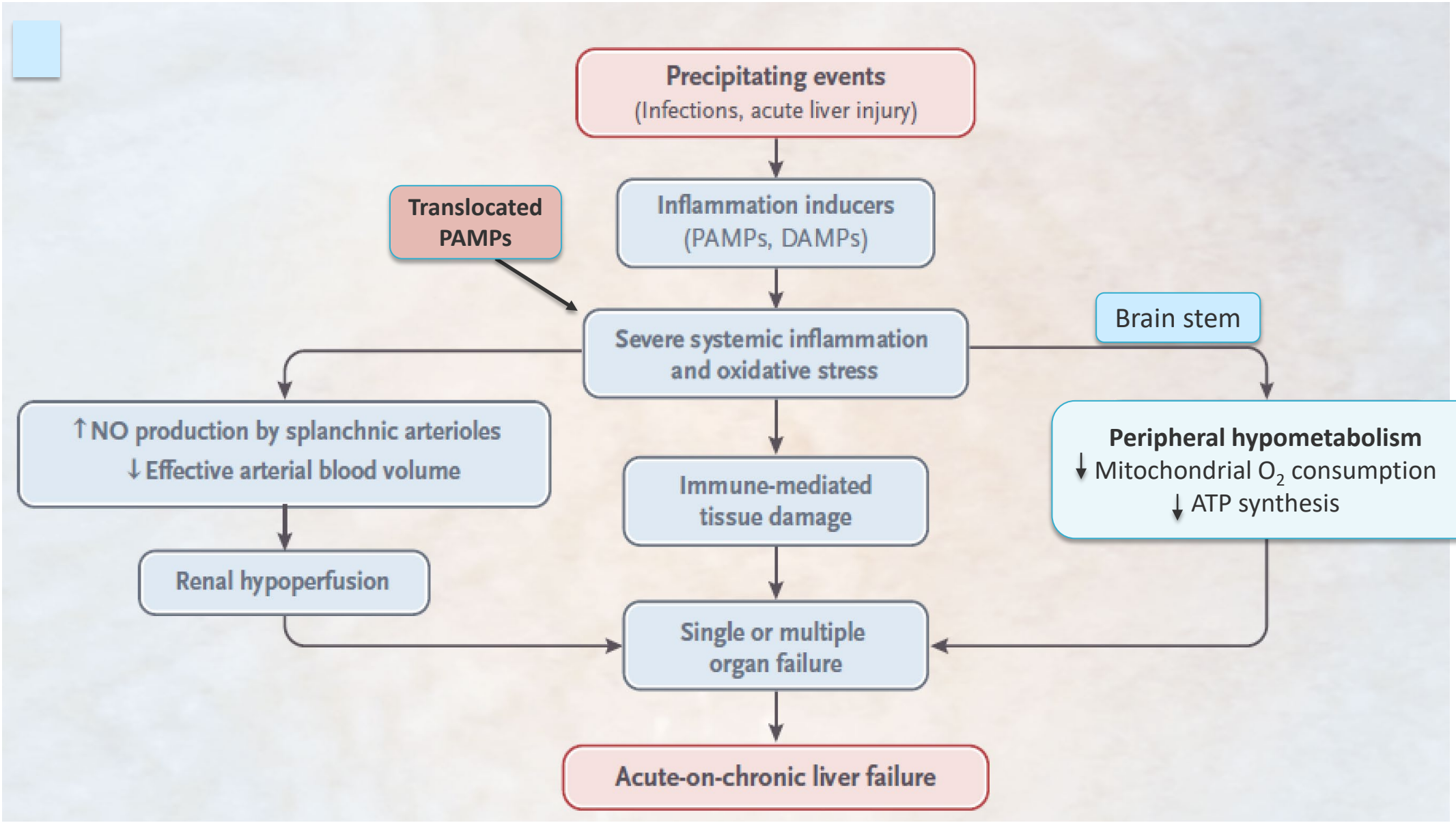
Systemic Inflammation

- **Assessed in blood: leukocyte count, CRP levels, cytokine levels**
  - **Exists in any form of acutely decompensated cirrhosis**
  - **Is more intense with ACLF than without ACLF**
  - **Is more intense in ACLF-3 than ACLF-1 or -2**
  - **Is less intense when ACLF improves**

Intense systemic inflammation is a major driver of ACLF development

Arroyo, Angeli, et al. J Hepatol 2021;74:670-85.

Model for ACLF Pathophysiology



Adapted from Arroyo et al. N Engl J Med 2020;382:2137-45.

Outline

- **Management**

Medical Management

Principles

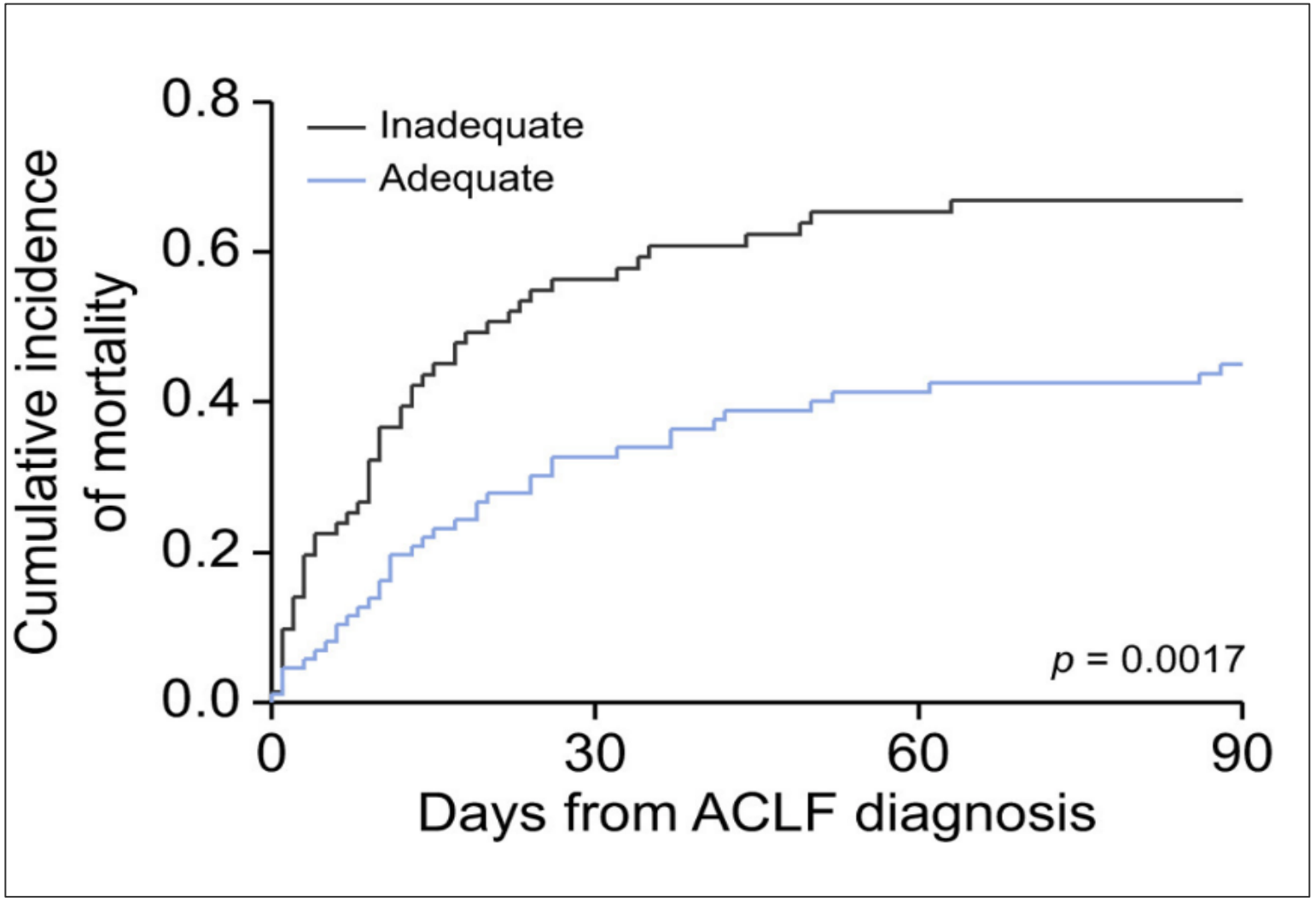
- Diagnose acute precipitants & treat them urgently
- Provide supportive Tx in ICU or intermediate care unit
- Objective: Bridge to liver transplantation

Arroyo et al. N Engl J Med 2020;382:2137-45. EASL CPG. J Hepatol 2023;79:461-91.

Treating precipitants

(acute infections, alcohol-related hepatitis)

Empiric Broad-Spectrum Antibiotics & Risk of Death Among Infected Patients with ACLF (PREDICT Study)



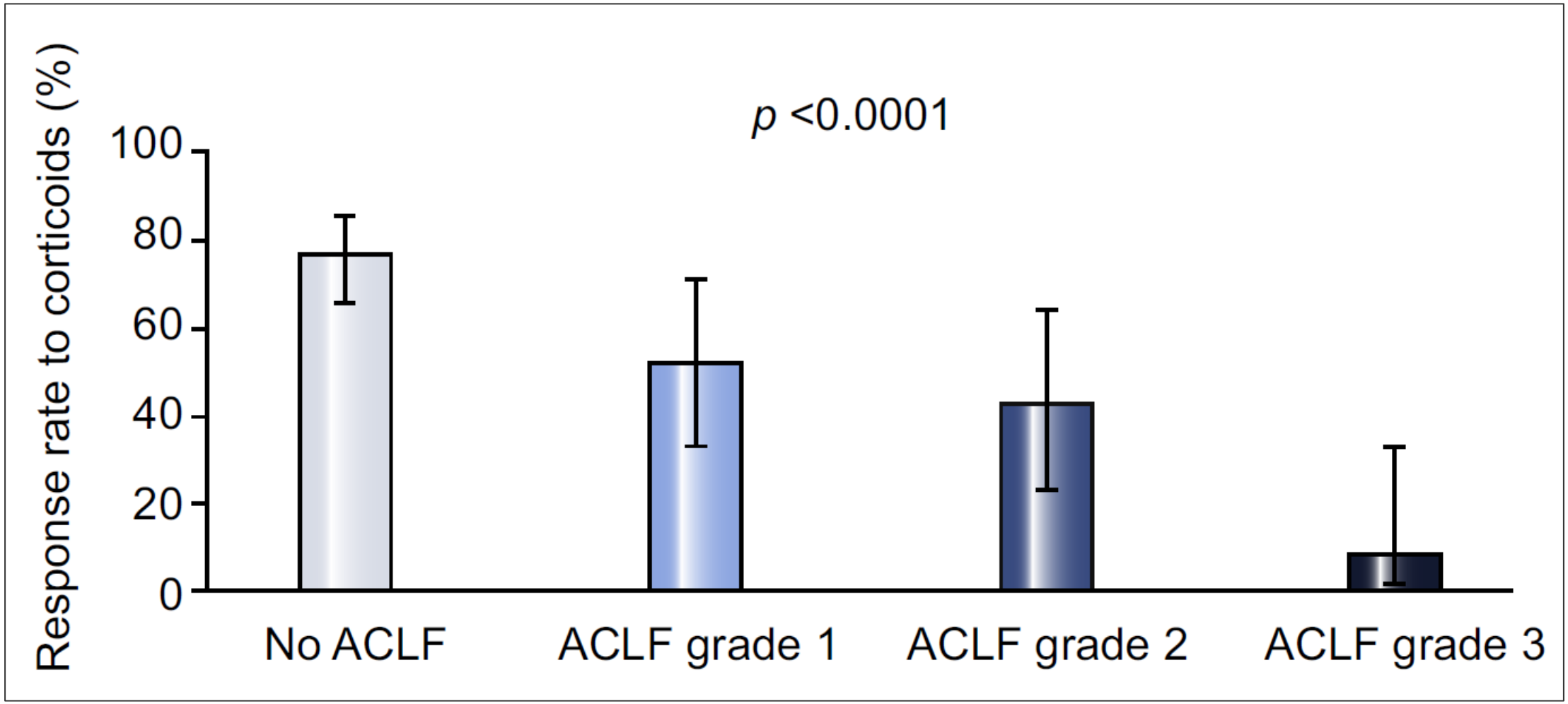
Trebicka, Fernandez, et al. J Hepatol 2021:74;1097-108.

EASL CPG Recommendation

- **Patients with ACLF and suspicion of bacterial infections should receive broad-spectrum, empirical antibiotic therapy according to local epidemiology as soon as possible.**

EASL CPG. J Hepatol 2023;79:461-91.

The Efficacy of Steroids for Alcohol-Related Hepatitis Depends on Baseline ACLF Grade



Sersté et al. J Hepatol 2018;69:318-24.

EASL CPG Recommendations

- Corticosteroids are not recommended in patients with ACLF-3 caused by alcohol-related hepatitis.
- Corticosteroids are also not recommended in patients with uncontrolled bacterial infection

EASL CPG. J Hepatol 2023;79:461-91.

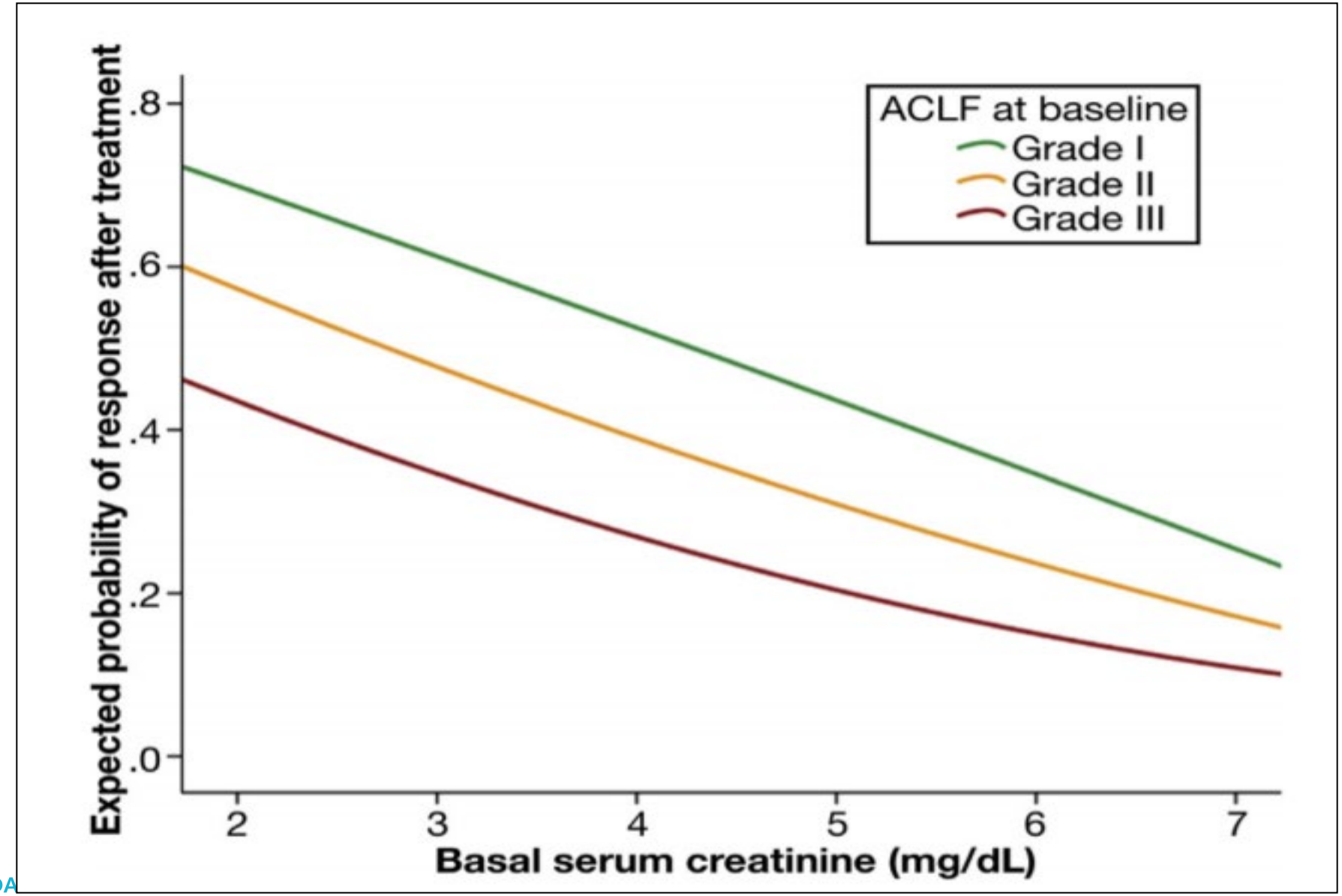
Supportive Therapies

EASL CPG Recommendations

- **The use of artificial or bioartificial extracorporeal liver support or plasma exchange in ACLF is not recommended outside investigative trials.**

EASL CPG. J Hepatol 2023;79:461-91.

Efficacy of Terlipressin for HRS-AKI Depends on Baseline Screat & ACLF Grade



EUROPEAN FOUNDA

Piano et al. Clin Gastroenterol Hepatol 2018;16:1792-1800.e3.

Site of Admission (EASL CPG)

- **ICU:**
  - **Need for organ support (vasopressors, mechanical ventilation, or RRT)**
  - **Massive bleeding**
  - **Grade III-IV hepatic encephalopathy (airway protection)**
  - **Septic shock**
  - **Time to admission: Within the first 6 h after diagnosis**
- **Intermediate care:**
  - **Variceal bleeding**
  - **Grade II-III hepatic encephalopathy**
  - **Sepsis with HRS-AKI or with liver or coagulation failures**

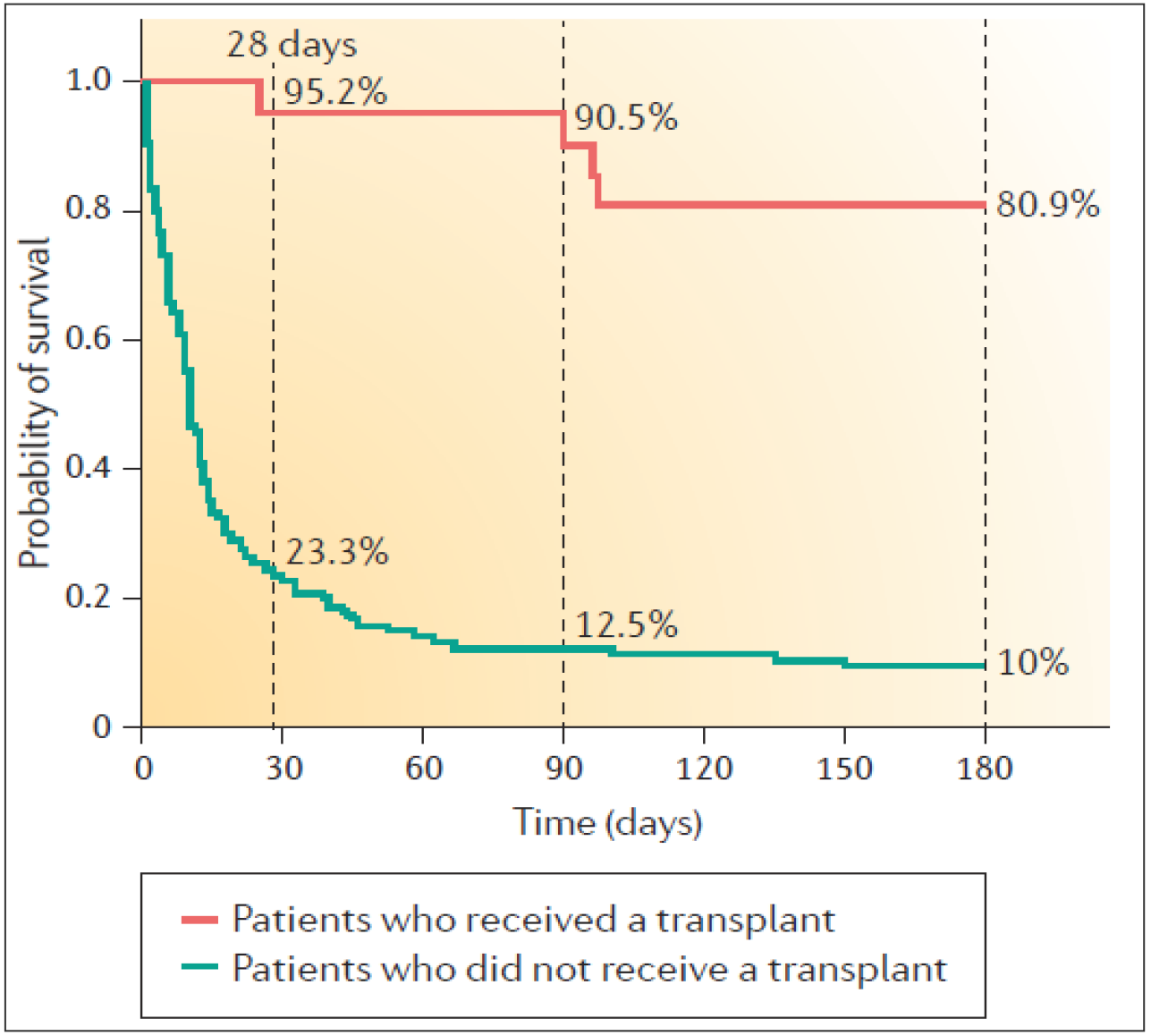
EASL CPG. J Hepatol 2023;79:461-91.

EASL CPG Recommendations

- **The risk of death should be evaluated 3-7 days after starting full organ support and not at admission**

EASL CPG. J Hepatol 2023;79:461-91.

6-Month Survival After Early (<28 days) Liver Transplantation for ACLF-2 or -3



Gustot, Fernandez, et al. Hepatology 2015;62:243-52.

EASL CPG Recommendations

- An early assessment for liver transplantation should be proposed for all patients with severe ACLF (ACLF-2 or -3).

- Defining criteria for futile liver transplantation in patients with ACLF-3 is an urgent medical need.

EASL CPG. J Hepatol 2023;79:461-91.

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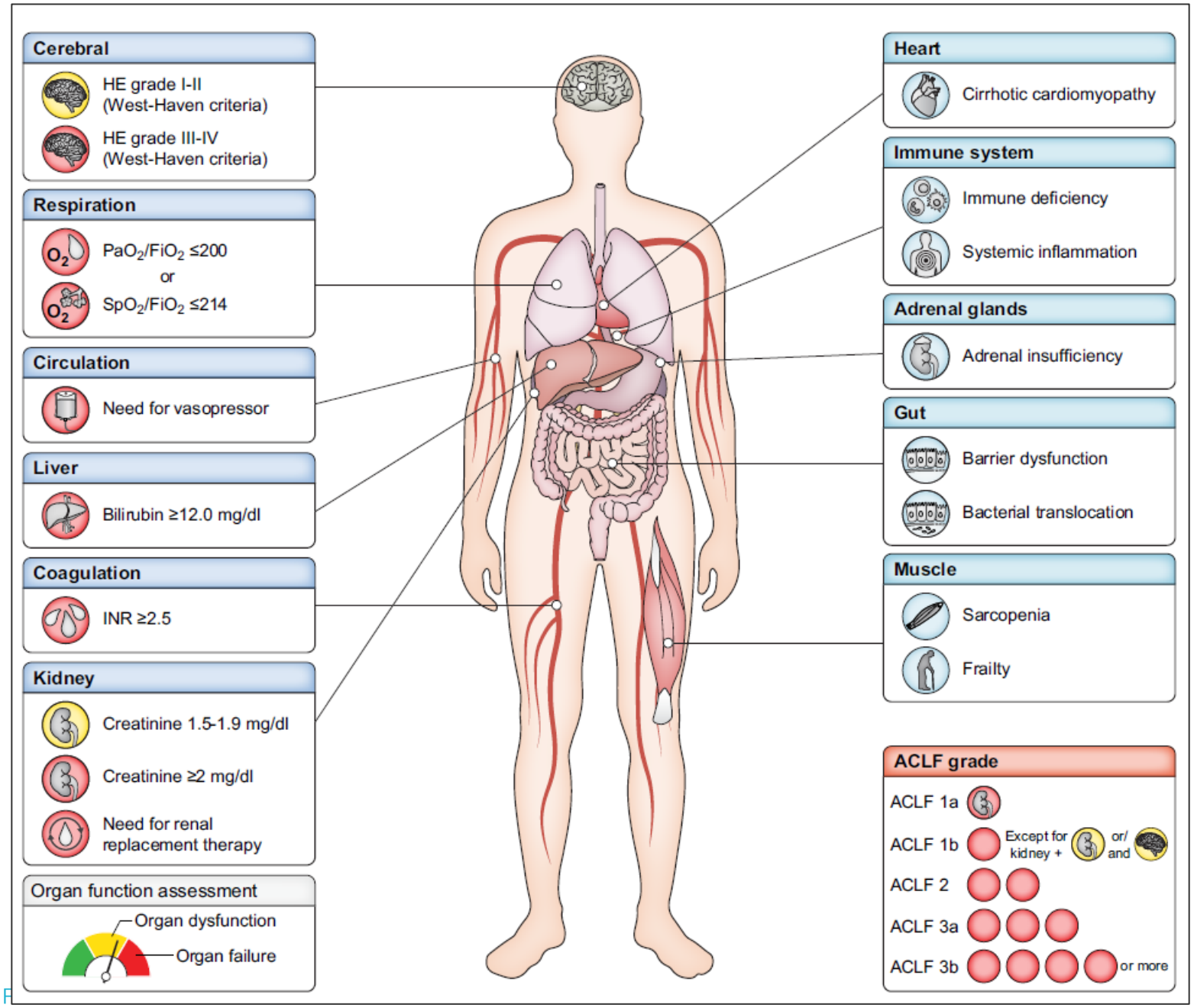

EASL CPG.
J Hepatol 2023;
79:461-91.

Conclusions

- The European definition of ACLF is evidence-based & widely used.
- ACLF is the most severe form of acutely decompensated cirrhosis.
- Systemic inflammation is a key pathogenic mechanism.
- Medical management should be urgently started against precipitants & failing organs.
- Early liver transplantation for ACLF-2, -3 seems effective but limited due to narrow time.
- The research agenda is busy.