Acute on Chronic Liver Failure

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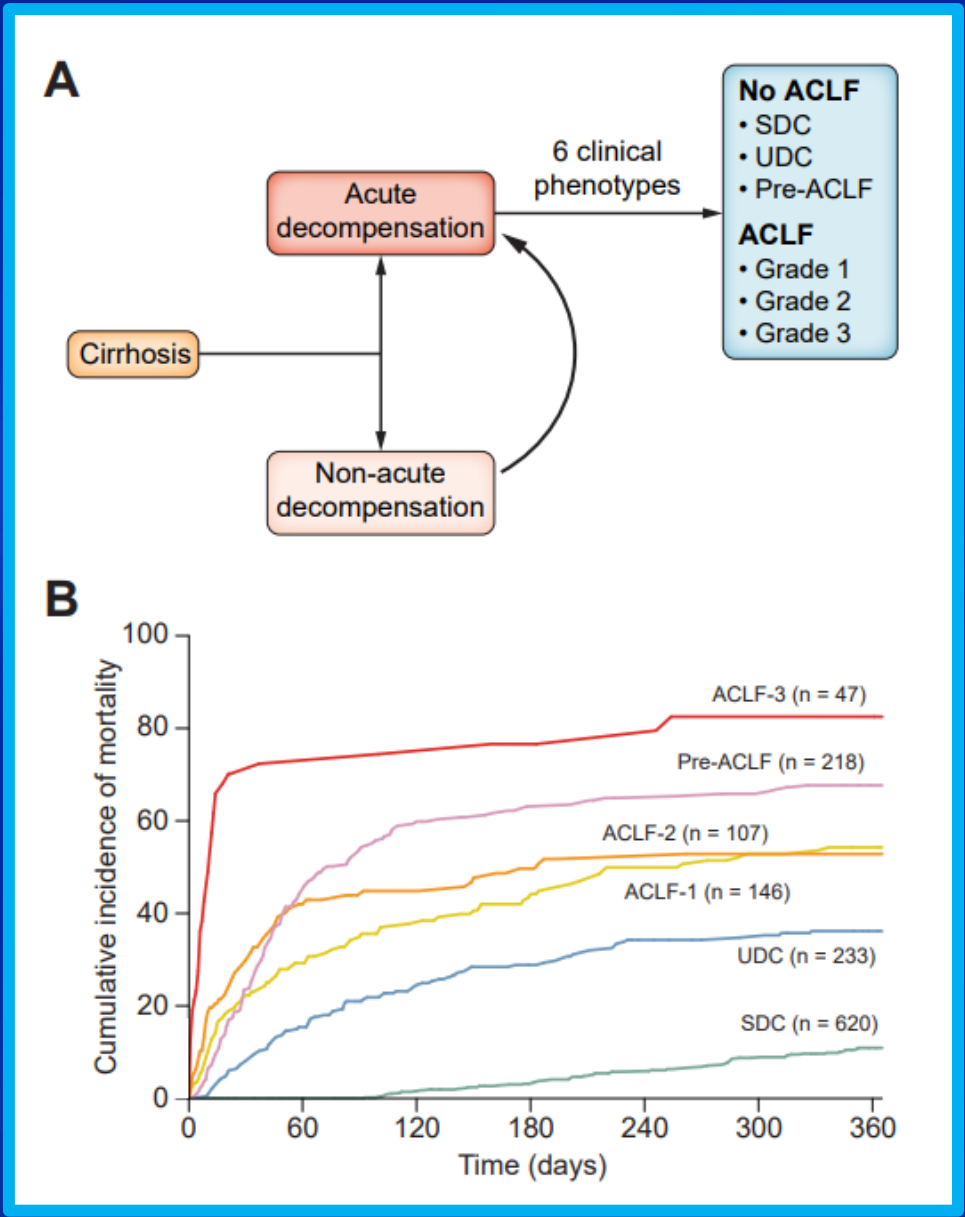
Phenotypes of Acute Cirrhotic Decompensation



SDC: Stable Decompensation
UDC: Unstable Decompensation
ACLF: Acute-on-Chronic Liver Failure

Acute-On-Chronic Liver Failure

World Gastroenterology Organization Consensus Definition

- Syndrome in patients with Chronic Liver Disease (with or without previously diagnosed cirrhosis), characterized by:
  - Acute Hepatic Decompensation resulting in Liver Failure (Jaundice and INR prolongation), and
  - One or more Extra-Hepatic Organ Failures, and
  - Associated with increased Mortality up to 3 months.
- Is different from traditional Cirrhosis Decompensation.

Acute on Chronic Liver Failure (ACLF)

- **Definition APASL (www.aclf.in):** acute hepatic insult in patient with (diagnosed or undiagnosed) chronic liver disease (without or with cirrhosis) causing bilirubin >/= 5 mg/dL and INR >/= 1.5, complicated within 4 weeks with ascites and/or PSE. http://www.aclf.in/?page=doctor_aarc_grade_cal
  - Excludes patients with prior "decompensation" who deteriorate and patients with bacterial infections.
  - Patient is at high risk of extra-hepatic multisystem organ failure.
  - "Golden window", were therapy can be started, precedes multisystem organ failure.
    - In Asia 80% are due to HBV.
    - Nucleoside analogs improve mortality if HBV-DNA decrease > 2 log within 2 weeks.
  - Asks for early detection and treatment of cerebral failure (PSE I-IV, and ammonia >/=75 mM/L as threshold for cerebral edema), renal failure (creatinine elevation >/= 0.3 mg/dL or >/= 1.5-fold over 48 h if >/= 0.7 mg/dL), Circulatory Failure (Lactate >/= 1.5), Coagulation Failure (INR >/= 1.8), and Liver Failure (Bilirubin >/= 15)
  - Considers >/= 2 organ failures as high risk for 28-d mortality.

Acute on Chronic Liver Failure (ACLF)

- **Definition EASL-CLIF (www.efclif.com):**
  - **Acute decompensation (AD)** of chronic liver disease (with cirrhosis) with development of large ascites, PSE, GI hemorrhage and/or bacterial infection,
  - **associated with at least 2 organ failures**, with one being kidney with a creatinine > 1.5 mg/dL,
  - leading to a 28-day mortality >/= (15% in study) 22% (in reality).
- **Group at highest risk:**
  - Patients with compensated cirrhosis or recently decompensated cirrhosis in the last 3 months.
    - Patients without prior decompensation develop more severe ACLF

Excludes: HCC outside Milan, HIV, Severe chronic extra-hepatic disease, Elective admission for procedure/treatment

http://www.clifresearch.com/ToolsCalculators.aspx

Organ Failure and Grading Definitions in ACLF

ORGAN FAILURE (% of ACLF)

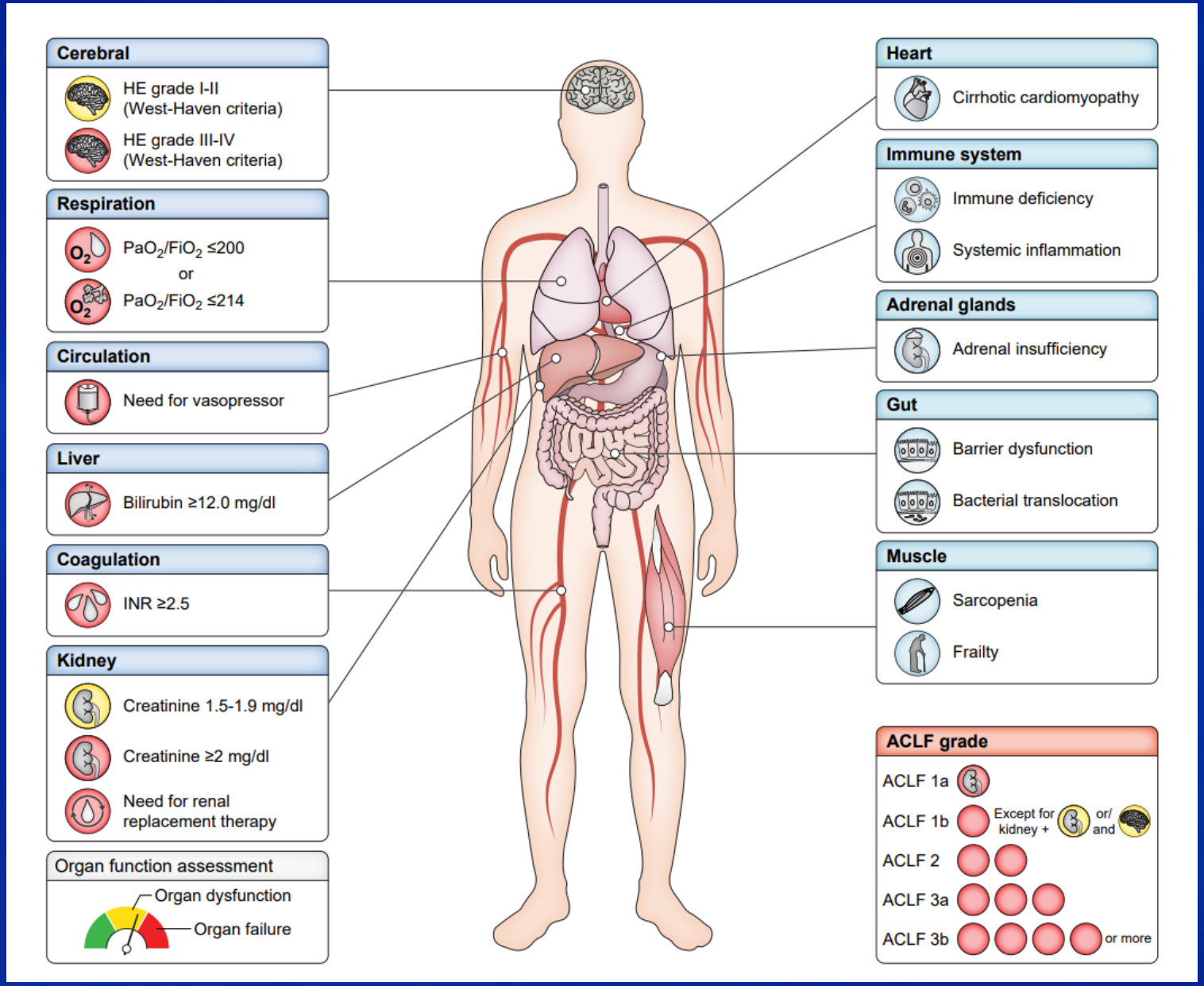
- **Coagulation (28%):** INR > 2.5 or plat < 20K (mortality OR 6.8)
- **Kidney (56%):** Creat > 2 mg/dL or Hemodialysis (mortality OR 6.3)
- **Liver (44%):** Bili > 12 mg/dL (mortality OR 3.9)
- **Brain (24%):** HE III or IV (mortality OR 3.9)
- **Lung (9%):** SpO_2/FiO_2 </= 214 or PaO_2/FiO_2 < 200 (mortality OR 2.8)
- **Circulation (17%):** need of inotropes (mortality OR 2.2)

GRADES OF ACLF (% of AD)

- **ACLF-1 (16%):** (28-d mort 22.1%)
  - renal failure (creat > 2 mg/dL), or
  - nonrenal organ failure associated with:
    - creatinine 1.5-1.99 mg/dL and/or
    - grade I-II encephalopathy
- **ACLF-2 (11%):** 2 organ failures (28-d mort 32%)
- **ACLF-3 (4%):** 3-6 organ failures, (28-d mort 73%)

48% had >/= 2 organ failures

Organ Systems Involved in ACLF



The risk of 28-day mortality in a patient with ACLF should be assessed sequentially to evaluate their response to intervention

NACSELD and APASL ACLF Research Consortium Scores underestimates 28-day and 90-day mortality

North American Consortium for the Study of End-Stage Liver Disease
NACSELD-ACLF

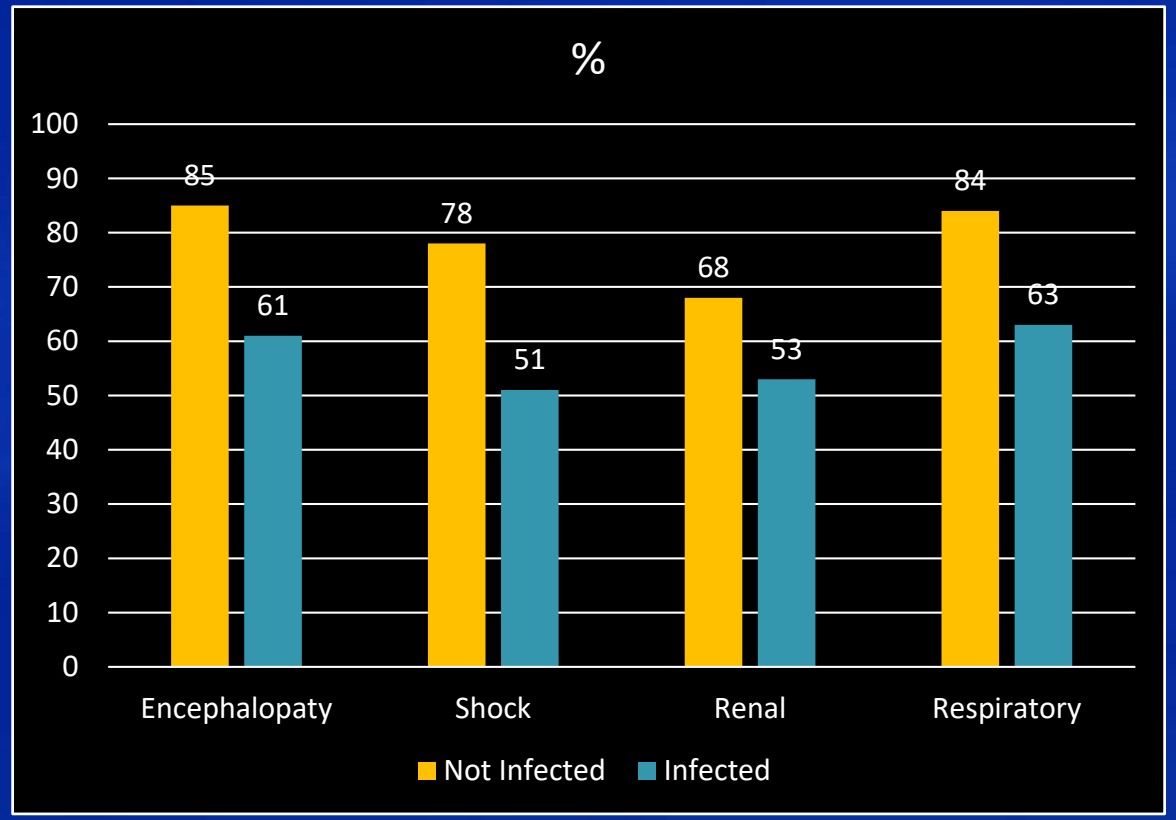
- Definition NACSELD (www.nacseld.org):
  - **Cirrhosis** with two or more organ failures of the four described:
    - **Brain failure**: Encephalopathy West-Haven grade 3 or 4.
    - **Renal failure**: need for renal replacement therapy.
      - This is different from acute kidney injury, which has recently been redefined by the International Ascites Club.
    - **Respiratory failure**: need for bilevel positive airway pressure (BIPAP) or mechanical ventilation.
    - **Shock**: need for pressor support, a mean arterial pressure <60 mm Hg, or a reduction of >40 mm Hg in systolic blood pressure from baseline despite adequate fluid resuscitation.

Excludes: Outpatient with infection, HIV infection, Prior organ transplant, disseminated malignancy
https://nacseld.org/calculator

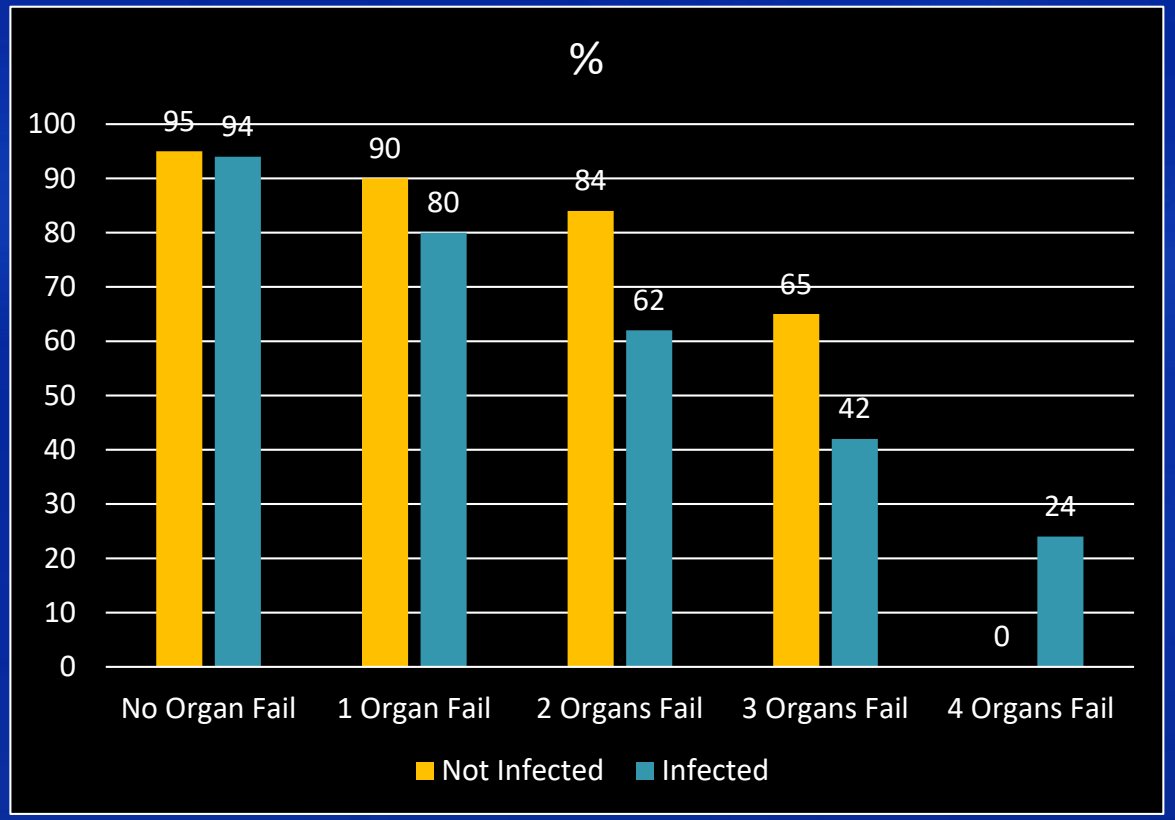
Survival at 30-days by Number of Organ Failures and Presence of Infection - NACSELD

Modified from: O'Leary JG et al. Hepatology. 2018 Jun;67(6):2367-2374

Survival at 30-days with One Organ Failure



Survival at 30-days by number of Organ Failures



Practical Operational Definitions

- ACLF is a potentially reversible condition in patients with chronic liver disease with or without cirrhosis that is associated with the potential for multiple organ failure and mortality within 3 months in the absence of treatment of the underlying liver disease, liver support, or liver transplantation.

- In patients with cirrhosis who are hospitalized with ACLF:
  - NACSELD score is likely associated with futility,
  - EASL-CLIF sequential organ failure assessment score is associated with 28-day prognostication and useful to prioritize for Liver Transplantation.

- Recent evidence suggests that continuing intensive care when the CLIF-C ACLF score is >/= 70 despite 48 hours of intensive care may be futile.

Comparison of Components Defining Organ Failures

Modified from: Lai JC (AASLD 2019)

Organ	APASL ACLF	EASL CLIF ACLF	NACSELD ACLG
Liver	Bilirubin **>/= 15 & 25 mg/dL**	Bilirubin **>/= 12 mg/dL**	-
Coagulation	PT/INR **>/= 1.8 & 2.5**	PT/INR **>/= 2.5**	
Kidney	Creatinine: increase > 0.3 or 1.5-fold over 48 h to: **>/= 0.7 & 1.5**	Creatinine **>/= 2 mg/dL** **Dialysis**	**Dialysis**
Brain	HE Grades **I-II & III-IV**	HE Grade **III-IV**	HE Grade **III-IV**
Circulation	Lactate **>/= 1.5 & 2.5**	**Vasopressors**	**Vasopressors**
Respiratory	-	PaO2/FiO2 **</= 200**, or SpO2/FiO2 **</= 214**	**Mechanical Ventilation**
AUROC for Mortality	**0.78**	**0.83**	**0.85**
	http://www.aclf.in/?page=doctor_aarc_grade_cal	http://www.clifresearch.com/ToolsCalculators.aspx	https://nacseld.org/calculator

In APSL, Grade 1 = 5-7 points; Grade 2 = 8-10 points; Grade 3 = 11 or more; Gets 1 point for each first definition value per organ, or 2 for each second incremental in the same organ.

Selection of Prediction Model by Scenario

Modified from: Lai JC (AASLD 2019)

	APASL ACLF	EASL CLIF ACLF	NACSELD ACLF
Patient Condition	No Cirrhosis, or Cirrhosis	Cirrhosis	
Primary Injury	Liver related (virus, alcohol, DILI, etc)	Non-Liver Related (Infection, Surgery, …)	
Clinical Goal	**Sequentially Assess Response to therapy Identify window for Transplant Identify patients for regenerative or liver-support therapy**		**Help discussions about Futility**

EASL-CLIF prognostic and diagnostic scores for ACLF

CLIF-C ACLF score for mortality prediction[1]*
10 x [0.033 x Clif OFs + 0.04 x Age + 0.63 x Ln(WBC) – 2]

Chronic liver failure – organ failure score system[1]			
Organ/system†	1 point	2 points	3 points
Liver (bilirubin, mg/dl)	<6	≥6–<12	**≥12.0**
Kidney (creatinine, mg/dl)	<2.0	**≥2.0–<3.5**	**≥3.5 or renal replacement**
Brain/HE (West Haven Criteria)	Grade 0	Grades 1–2	**Grades 3–4‡**
Coagulation (INR, PLT count)	<2.0	≥2.0–<2.5	**≥2.5**
Circulation (MAP, mmHg and vasopressors)	≥70	<70	**Use of vasopressors**
Lungs PaO_2/FiO_2, or	>300	≤300–>200	**≤200§**
SpO_2/FiO_2	>357	>214–≤357	**≤214§**

*Age in years, creatinine in mg/dL, WBC in 10^6 cells/L, sodium in mmol/L;
†Bold text indicates the diagnostic criteria for organ failures; ‡Patients submitted to mechanical ventilation due to HE and not to a respiratory failure were considered as presenting a cerebral failure (cerebral score = 3); §Other patients enrolled in the study with mechanical ventilation were considered as presenting a respiratory failure (respiratory score = 3)

1. Jalan R, et al. J Hepatol 2014;61:1038–47;
EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024

Sub-Types of ACLF

- By underlying Liver Disease Severity:
  - Type A: over Chronic liver disease without cirrhosis.
  - Type B: over Compensated Cirrhosis.
  - Type C: over Decompensated Cirrhosis
- By Trigger:
  - Infection related.
  - Non-infection related.
  - Hepatic injury (HAV, HEV, HBV, AIH, Wilson, alcohol, drug hepatotoxicity …)
  - Extra-hepatic injury (Infection, GI bleed, surgery, …)

Triggers of ACLF

Modified from: Arroyo V et al. J Hepatol 2015;62:S131-s143

- Bacterial infection (39%) (most common SBP & pneumonia)
- Alcohol (23%)
- GI bleed (18%) (if causes jaundice & coagulopathy)
- Drug or Herbal therapy/CAM.
- AIH flare-up
- Wilson disease flare-up

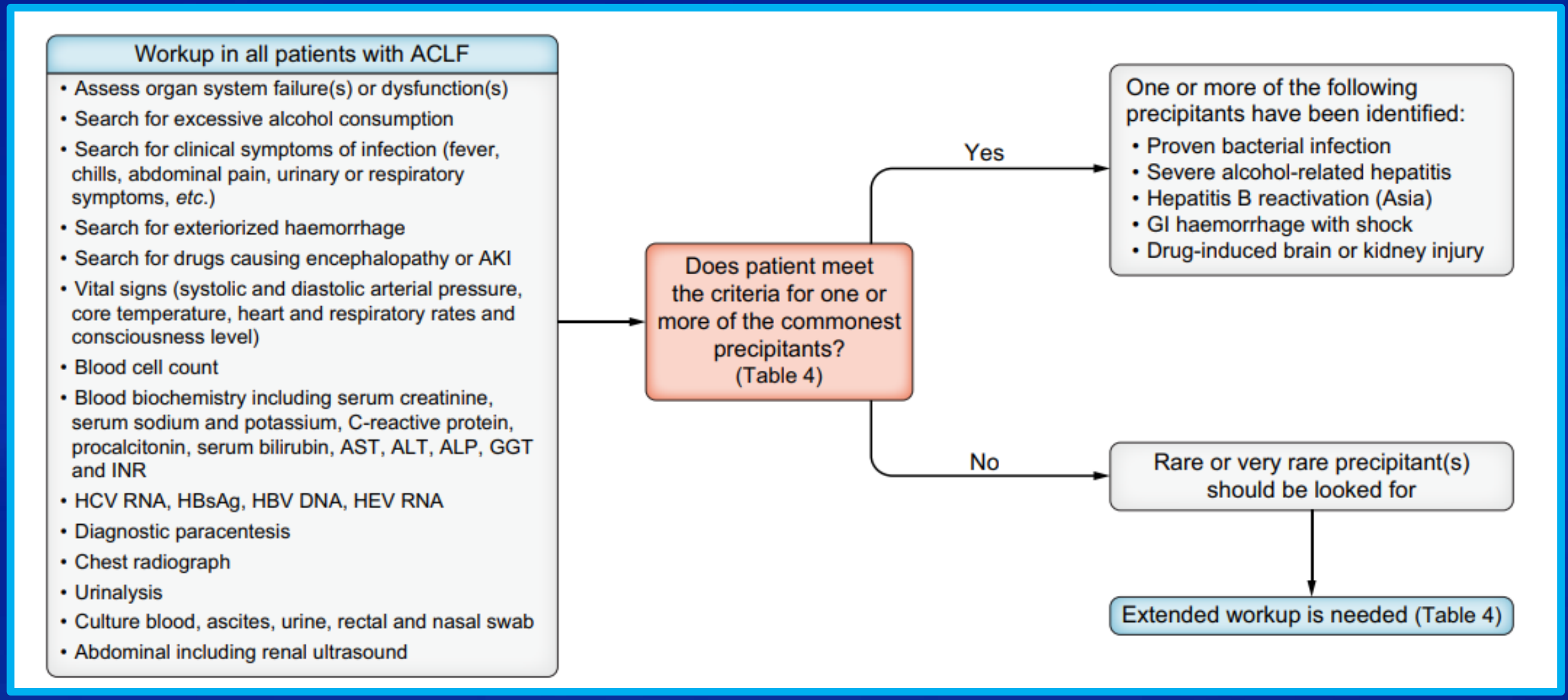
Most common cause in children

- HBV flare-up (HBV-DNA > $2x10^4$ IU/mL)
- HEV

- HAV/HCV/HDV
- Non-bacterial Infection
- Sepsis
- TIPS
- Paracentesis without albumin
- Surgery
- Other
- No precipitating factor: 43%

More than 1 trigger in 30%

Initial Work-Up for ACLF



Common Precipitants of ACLF

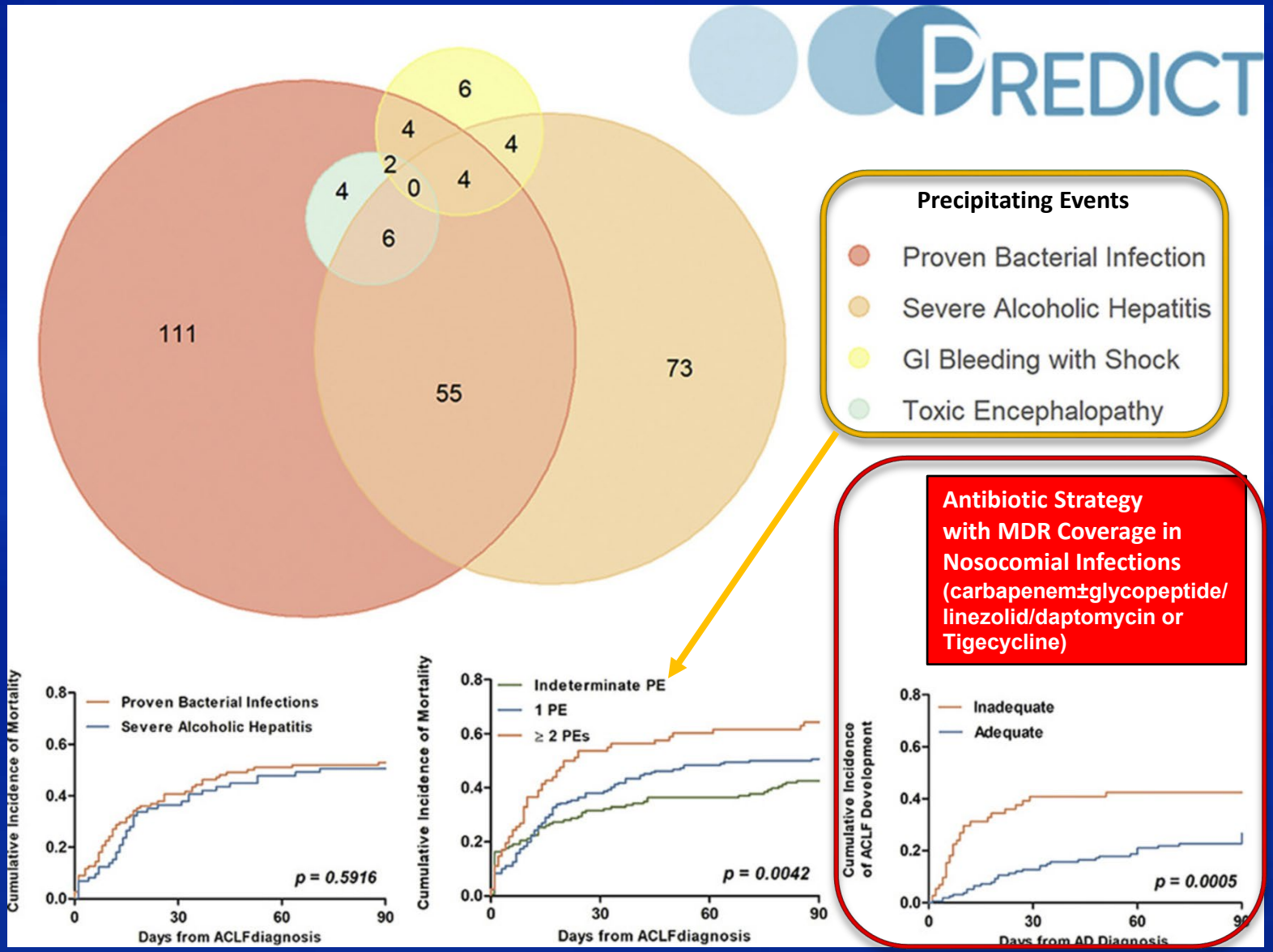
Common precipitants[a,b]	
Proven bacterial infection	
Spontaneous bacterial peritonitis	Neutrophils in ascites ≥250/mm^3
Spontaneous bacterial empyema	Hydrothorax and no evidence of pneumonia on chest imaging and neutrophils in pleural fluid >500/mm^3 plus negative pleural fluid culture or positive pleural fluid culture and neutrophils in pleural fluid ≥250 cells/mm^3
Spontaneous/secondary bacteraemia	Spontaneous bacteraemia: positive blood cultures and no cause of bacteraemia; secondary bacteraemia: (1) catheter-related infection (positive blood and catheter's tip cultures); (2) bacteraemia occurring within 24 hours after an invasive procedure
Urinary tract infection	Abnormal urinary sediment (>10 leukocytes/field) and positive urinary culture or uncountable leukocytes per field if negative cultures
Pneumonia	Clinical features of infection and new infiltrates on chest imaging
Bronchitis	Clinical features of infection, no infiltrate on chest imaging and positive sputum culture
Skin and soft tissue infection	Clinical features of infection associated with swelling, erythema, heat, and tenderness in the skin
Cholangitis	Cholestasis, right upper quadrant pain and/or jaundice and radiological data of biliary obstruction
Secondary peritonitis	Neutrophils in ascites ≥250/mm^3 frequently ≥10,000/mm^3), and at least two of the following: low glucose levels (<50 mg/dl [2.8 mmol/L]), protein concentration >10 g/L and LDH levels >normal serum concentration (Runyon's criteria). High amylase and bilirubin levels in ascites and Gram's stain showing polymicrobial infection in the presence of gut perforation. Evidence of an intra-abdominal source of infection (abdominal computed tomography or surgery)
Clostridioides difficile infection	3 unformed stools or more, toxigenic *Clostridiodes difficile* in stool
Fungal infection	
Invasive candidiasis	Isolation of *Candida* species in one blood culture or more (candidemia) or from normally sterile body fluids (*e.g.* ascites, pleural fluid)
Probable invasive aspergillosis	Detection of *Aspergillus* by direct examination and/or culture of respiratory samples in the presence of radiological imaging compatible with lung infection
Alcohol-related hepatitis	Active alcohol consumption and - If liver biopsy is unavailable, use NIAA criteria, *i.e.*, presence of 3 of the following criteria: 1. Serum bilirubin > 3 mg/dl [>50 μmol/L] 2. AST >50 IU/ml 3. AST/ALT ratio >1.5 4. AST and ALT < 400 IU/ml - Liver biopsy: Macrovesicular steatosis with ≥1 of the following: neutrophil infiltration, hepatocyte injury (ballooning), and Mallory-Denk bodies. The presence of megamitochondria, satellitosis (neutrophils surrounding dying/dead hepatocytes), and cholestasis (bilirubinostasis) is common, and may relate to prognosis.
Gastrointestinal hemorrhage with shock	Hematemesis, melena, low haemoglobin levels, sudden decrease in haemoglobin levels (≥2 g/dl), or any combination of these disorders, and hypovolemic shock; endoscopy
Drug-induced brain injury	Medical history of recent administration of sedative, mainly benzodiazepines, or opioids compounds
Drug-induced acute kidney injury	Medical history of administration of nephrotoxic drugs or compounds: NSAIDs, renin-angiotensin-aldosterone antagonists, α1-adrenoceptor antagonists, IV contrast media or nephrotoxic antibiotics (*i.e.*, vancomycin, aminoglycosides) (a comprehensive list of drugs is provided in Tables S1)

Rare Precipitants of ACLF

Rare precipitants	
Extrahepatic	
Viral infection	
Epstein-Barr virus (EBV)	AST and ALT >x3 ULN IU/ml Viral Capsid Antigen (VCA)-IgM antibody, Early Antigen (EA-D) antibody, Epstein-Barr Nuclear Antigen (EBNA) antibody, EBV quantitative PCR
Cytomegalovirus (CMV)	AST and ALT >3x ULN IU/ml CMV IgG antibody CMV quantitative PCR
Herpes simplex virus (HSV 1, 2, 6)	AST and ALT >1,000 IU/ml, HSV 1 and 2 IgM antibodies, HSV qualitative PCR
Varicella zoster virus (VZV)	AST and ALT >1,000 IU/ml, VZV IgM antibodies, qualitative PCR
Human immunodeficiency virus (HIV)	Mild elevations of AST and/or ALT, HIV-1/-2 antibodies, quantitative PCR
Parvovirus B19	AST and ALT >3-5 ULN IU/ml, parvovirus B19 IgM, qualitative PCR
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	Mild elevations of AST and/or ALT, positive PCR or rapid antigenic tests in respiratory samples
Influenza A, influenza B, syncytial respiratory virus	Mild elevations of AST and/or ALT, positive PCR in respiratory samples
Parasitic infection	
Visceral Leishmaniasis	Elevations of AST, ALT, AP and GGT, detection of Leishmania, parasite or DNA, in tissues of relevance (bone marrow aspirate> lymph nodes >liver biopsy; stain, PCR or culture) and serology (positive IgG and IgM antibodies)
Surgical or radiological intervention	Recent surgery or invasive radiological intervention (7-day time frame)
Intrahepatic	
Viral infection	
Hepatitis B virus (HBV) infection or reactivation	Elevated AST and ALT, elevated HBV DNA, elevated HBsAg (negative in S-variants), 10-25% positive anti-HBc IgM
Superimposed hepatitis D in patients with chronic HBV	AST and ALT >400 IU/ml, positive HDV IgM and IgG, elevated PCR (HDV RNA)
Superimposed hepatitis A	AST or ALT >400 IU/ml, serum bilirubin > 3 mg/dl (>50 µmol/L) and positive anti-HAV-IgM
Superimposed hepatitis E	AST and ALT >400 IU/ml, serum bilirubin > 3 mg/dl, anti-HEV-IgM (and IgG) and quantitative PCR (HEV RNA)
Superimposed hepatitis C	AST or ALT >400 IU/ml, serum bilirubin >3 mg/dl (>50 µmol/L) and elevated HCV RNA
Drug-induced liver injury (DILI)	Medical history of administration of hepatotoxic compounds, (drugs, over-the-counter medicine (OTCM) or herbals; check in LiverTox® ALT ≥5x ULN, ALT ≥3x ULN, ALP ≥2x ULN, plus bilirubin >2x ULN. Pattern of liver injury is classified according to R (ALT x ULN/ALP x ULN): hepatocellular: R≥5, cholestatic: R≤2 or mixed: 2>R<5. Liver biopsy is only required in sporadic cases
Wilson's disease	First manifestation of the disease or consequence of an abrupt discontinuation of the chelation therapy or of a superimposed viral hepatitis Leipzig criteria (Leipzig Scoring System[c]), high serum bilirubin levels (≥10 mg/dl, mainly indirect form), Coombs-negative haemolysis, mild-to-moderate rise of liver enzymes (<500 IU/ml), AST to ALT ratio >2.2, low serum ALP, ALP to total bilirubin ratio <4, severe coagulopathy, mild-moderate encephalopathy and altered copper metabolism indicated by low serum ceruloplasmin levels (<20 mg/dl) and high 24-hour cooper urinary excretion (>100 µg; usually > 500 µg/24h)
Flare of autoimmune hepatitis (AIH)	Medical history of non-adherence to immunosuppressive therapy, de-escalation of immunosuppressive therapy or postpartum period. Elevated levels of AST, ALT, hypergammaglobulinemia and increased IgG; positive (≥1/80) ANA, anti-SMA, anti-SLA/LP in type 1 AIH; anti-LKM 1 and 3, anti-LC-1 in type 2 AIH. Histological examination of liver biopsy specimens is not mandatory in case of previously established diagnosis but can aid differential diagnosis in case of response to a second exogenous insult (*e.g.*, viral or drug related hepatitis) on top of typical AIH. Hyperacute exacerbation of undiagnosed or misdiagnosed AIH can be possible. Liver biopsy is mandatory for the diagnosis and also in the assessment of seronegative cases with no hypergammaglobulinemia and normal IgG. Histological features may differ from "typical characteristics of AIH"[d] and seronegativity is highly possible early in acute AIH. Simplified AIH score is unreliable in AIH with liver failure.
Ischaemic hepatitis	High peak of AST and ALT (usually >1,000 IU/ml), serum bilirubin usually <3 mg/dl and deep coagulopathy (marked increase in INR that improves rapidly) Abdominal ultrasonography must confirm vascular patency. Echocardiography with evaluation of right and left ventricular function

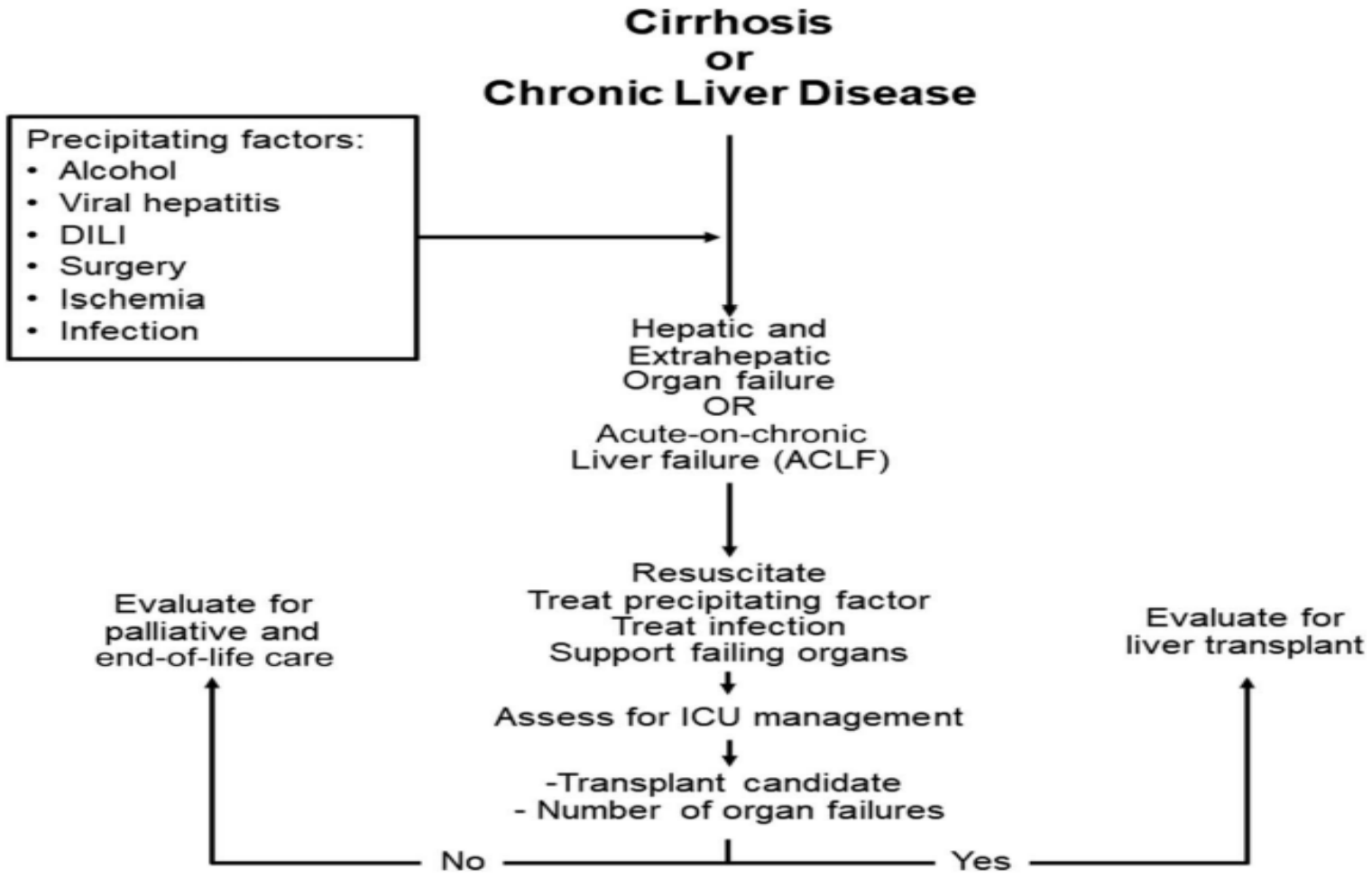
Effect of Precipitating Events (PE) in ACLF Mortality

Trebicka J. et al. J. Hepatology November 19, 2020 DOI: https://doi.org/10.1016/j.jhep.2020.11.019



PE = Precipitating Events

Course of ACLF



Presentation and Evolution

- Of the patients with “acute decompensation” (AD):
  - Only 20-22.5% have ACLF at admission
    - 11% develop ACLF during hospitalization (31-33.5% of all AD patients);
    - Predictors: Hb < 9.8, WBC > 5.6, MELD > 13, and Nosocomial Infection.
  - 77.5% do not have ACLF at admission, and they have a 28-day mortality of 4.7%
    - Mortality is 1.9% if they never develop ACLF (66.5% of all AD patients)
- Presence or absence of “precipitating event” does not affect ACLF mortality.
- Bilirubin >/= 12 mg/dL at diagnosis of ACLF is an independent predictor of severity.
- Of the patients with ACLF, 48% will have >/= 2 organ failures (ACLF >/= 2).

Presentation and Evolution

- Mortality Increases with the Grade of ACLF.
- Mortality is most dependent from its initial Clinical Course than its initial Grade.
  - 50% improve,
  - 30% have fluctuating or steady course, and
  - 20% worsen.
- Lower grades of ACLF are more likely to resolve than higher grades.
- Only 40% of ACLF will resolve completely, and most will likely survive (88-97%).
  - ACLF-1: 55%, ACLF-2: 35%; ACLF-3: 16%
- Most patients who progress to (or remain in) ACLF-3 will likely die (88-97%).

Presentation and Evolution

- Of patients with ACLF-1 at time of diagnosis (11% of AD),
  - 55% improve to “no ACLF”, with survival of 93%.
  - 30% worsen to ACLF-3, with mortality of 88%.
- Of patients with ACLF-2 at time of diagnosis
  - 35% improve to “no ACLF” with survival of 97%.
  - 26% worsen to ACLF-3, with mortality of 91%
- Of patients with ACLF-3 at time of diagnosis (3.5% of AD),
  - 16% improve to “no ACLF”, with survival of 88%.
  - 68% do not improve, with mortality of 97%.

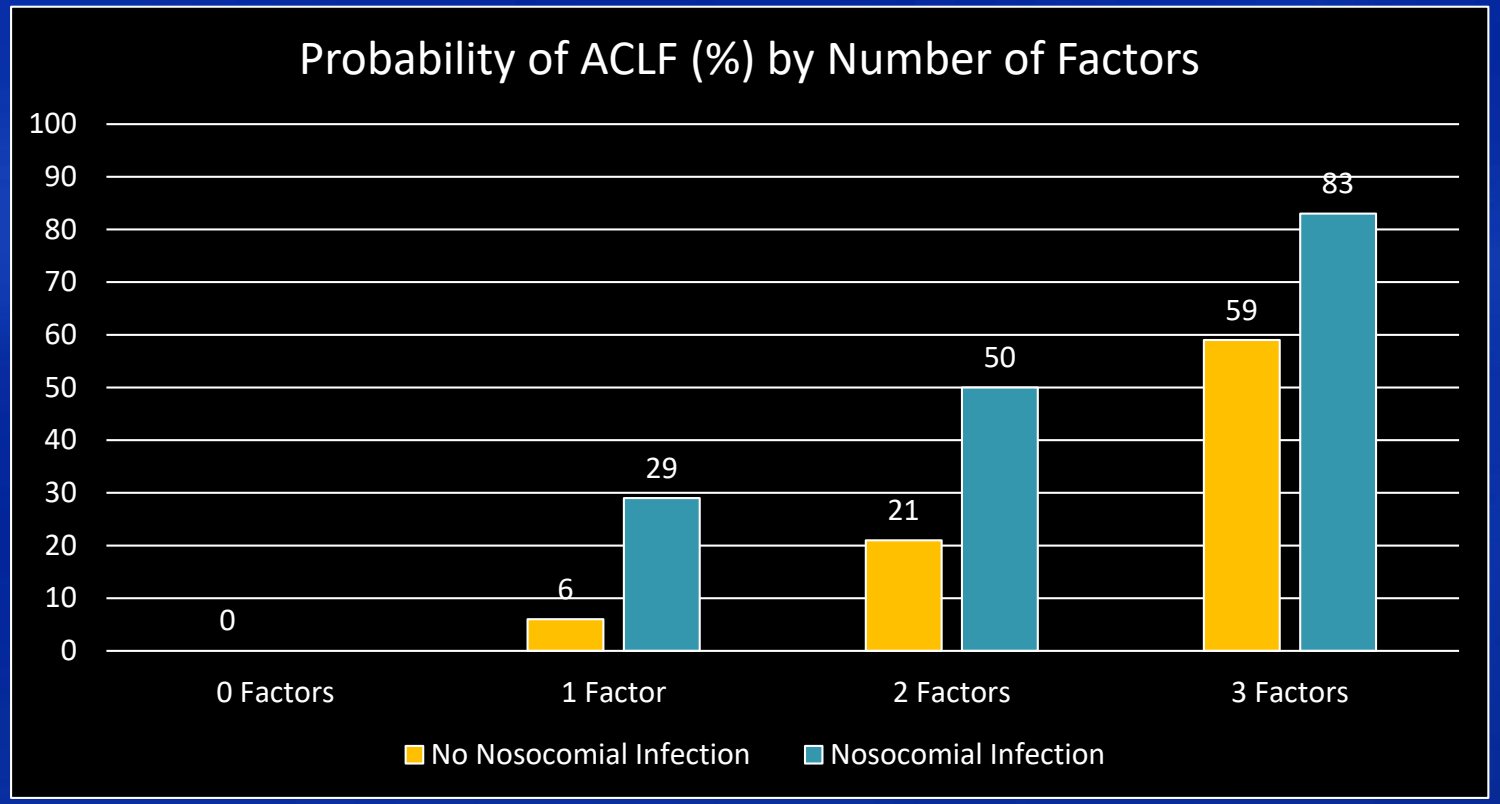
Prediction of Nosocomial CLIF-ACLF in patients admitted for Acute Decompensation of Cirrhosis

Modified from: Zaccherini G et al. JHEP Reports 2019

Factors at Time of Hospital Admission

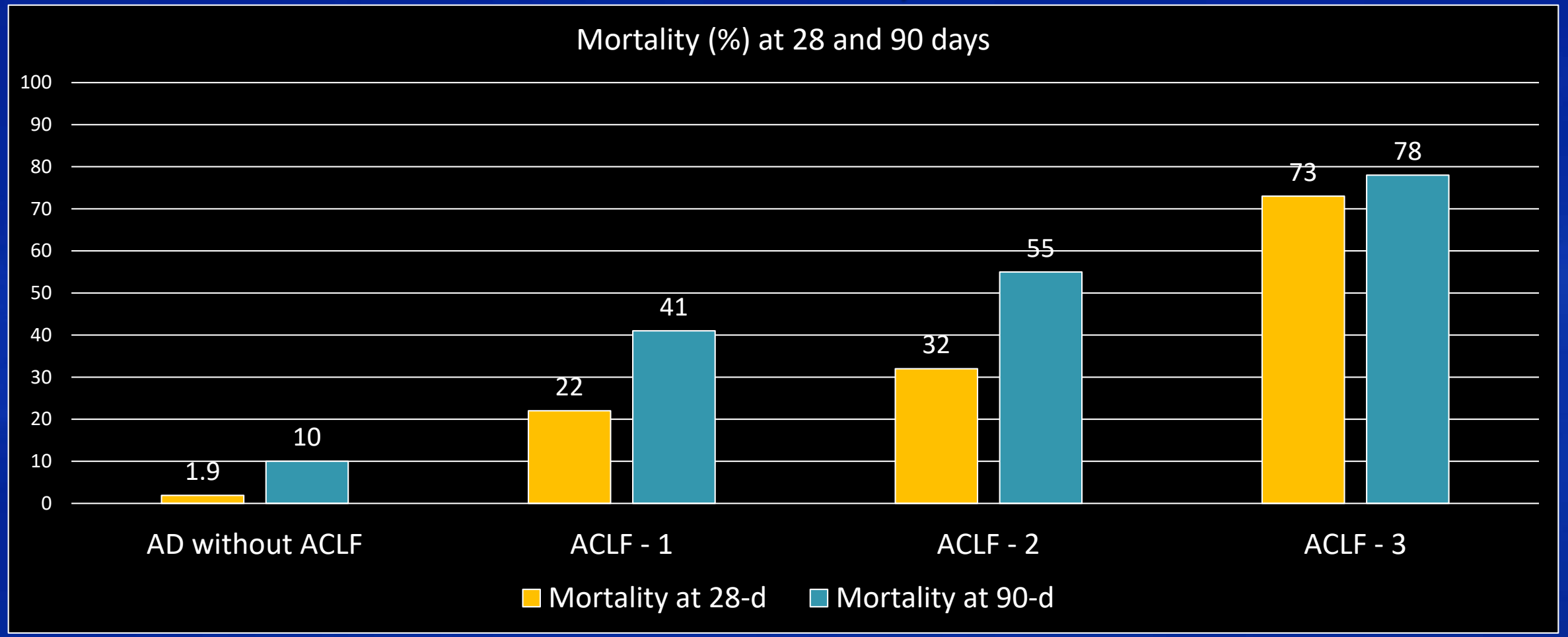
Factors
MELD > 13
Hemoglobin < 9.8 g/dL
Leucocytes > 5.6 x 10^9/ L

Effect of Nosocomial Infection on Risk of Nosocomial ACLF



Mortality of CLIF-ACLF by Grade

28 and 90 days



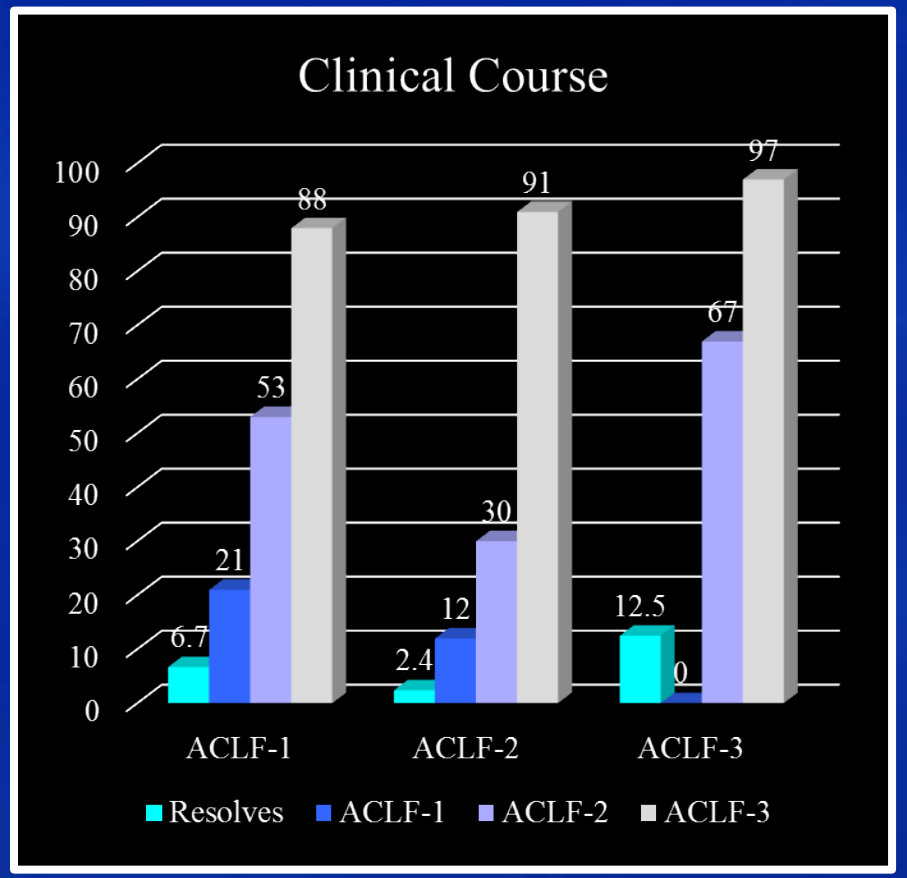
Clinical Course and Mortality of ACLF by Progression vs Regression

Gustot T et al. Hepatology 2015;

Clinical Course

	Resolves	Improves	Steady or fluctuates	Worsens
ACLF-1	55%	N/A	24%	21%
ACLF-2	35%	14%	26%	26%
ACLF-3	16%	16%	68%	N/A

28-day Mortality (%)



ACLF Evolving Concepts

- Infection-associated ACLF is the one with evidence of infection before admission or within 48 h of admission.
- 2 of 3 of ACLF are not associated with bacterial infection.
  - 43% have not recognized cause.
- Mortality is slightly lower in non-infection cases.
- Mortality @ 28-days is the same from extra-hepatic vs hepatic insult (48-50%)
- Later, extra-hepatic injury has higher mortality than hepatic injury:
  - 90-d mortality (68% vs 59%) and
  - 1-year mortality (75% vs 64%).

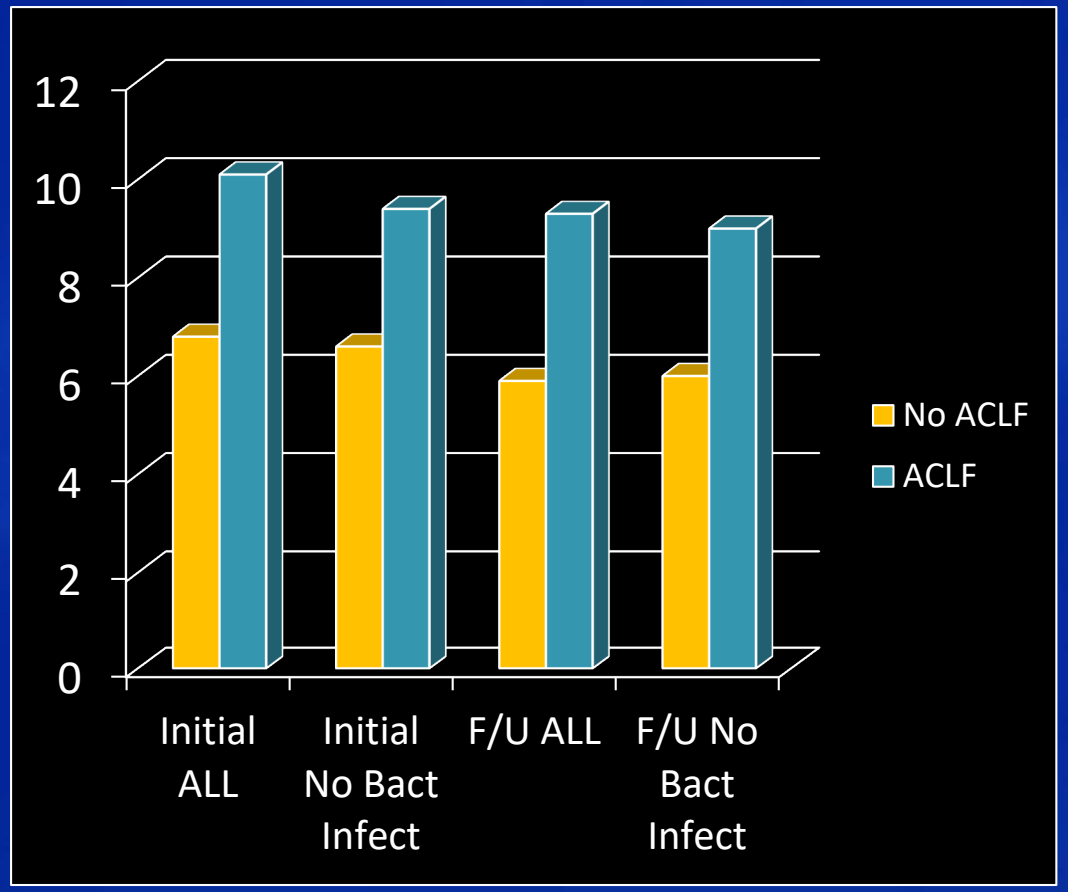
ACLF Evolving Concepts

- Infected and Non-infected patients have high WBC and CRP (both even higher in infected ones) indicating **SYSTEMIC INFLAMMATION**.
- 81% of ACLF develop SIRS within 7 days (1-week window)
  - 24% by day 4 + 57% more by day 7.
- IS IMPORTANT TO RE-CALCULTE ACLF SCORE DAILY TO ASSESS EVOLUTION AND THERAPY.

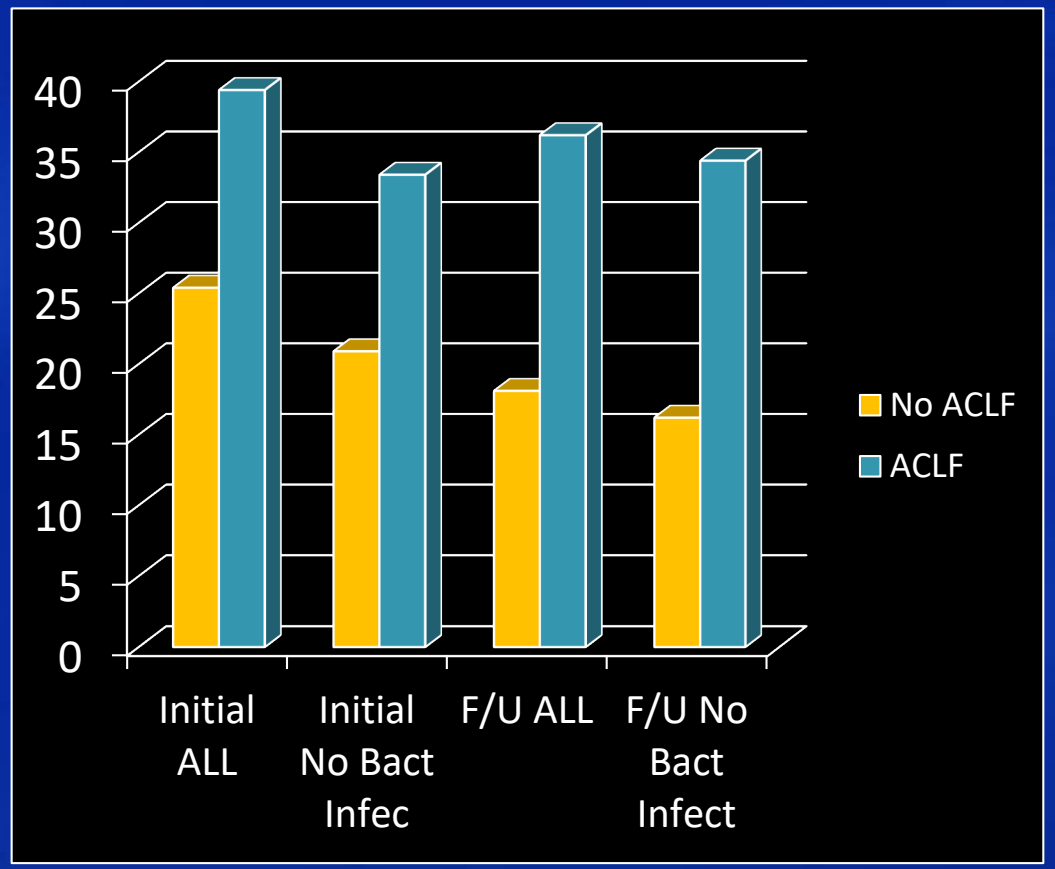
Leukocyte Count and CRP in CANONIC STUDY

Moreau R et al. J Clin Exp Hepatol 2014;5:81-85)

Leukocyte count
(x 10^9/L)



C-Reactive protein
(mg/L)

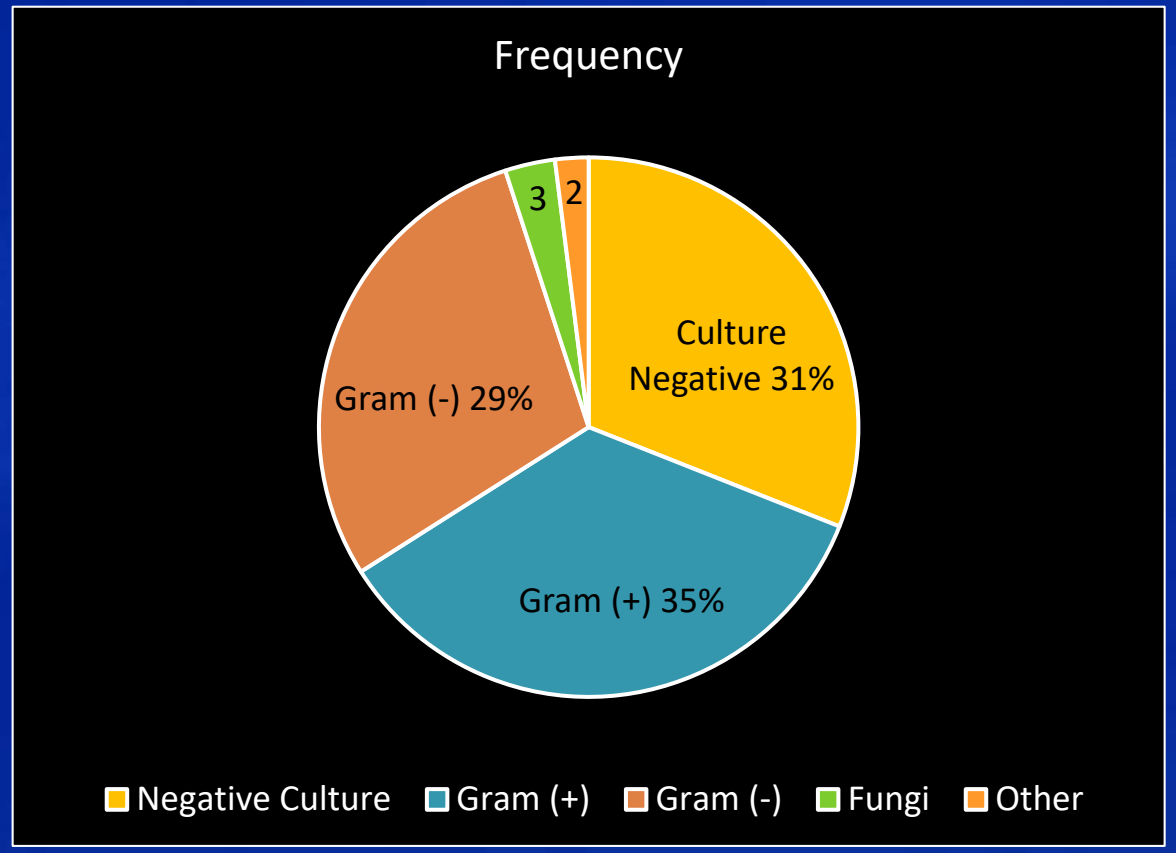


Inflammatory markers are high in ACLF compared with other Decompensated Cirrhosis

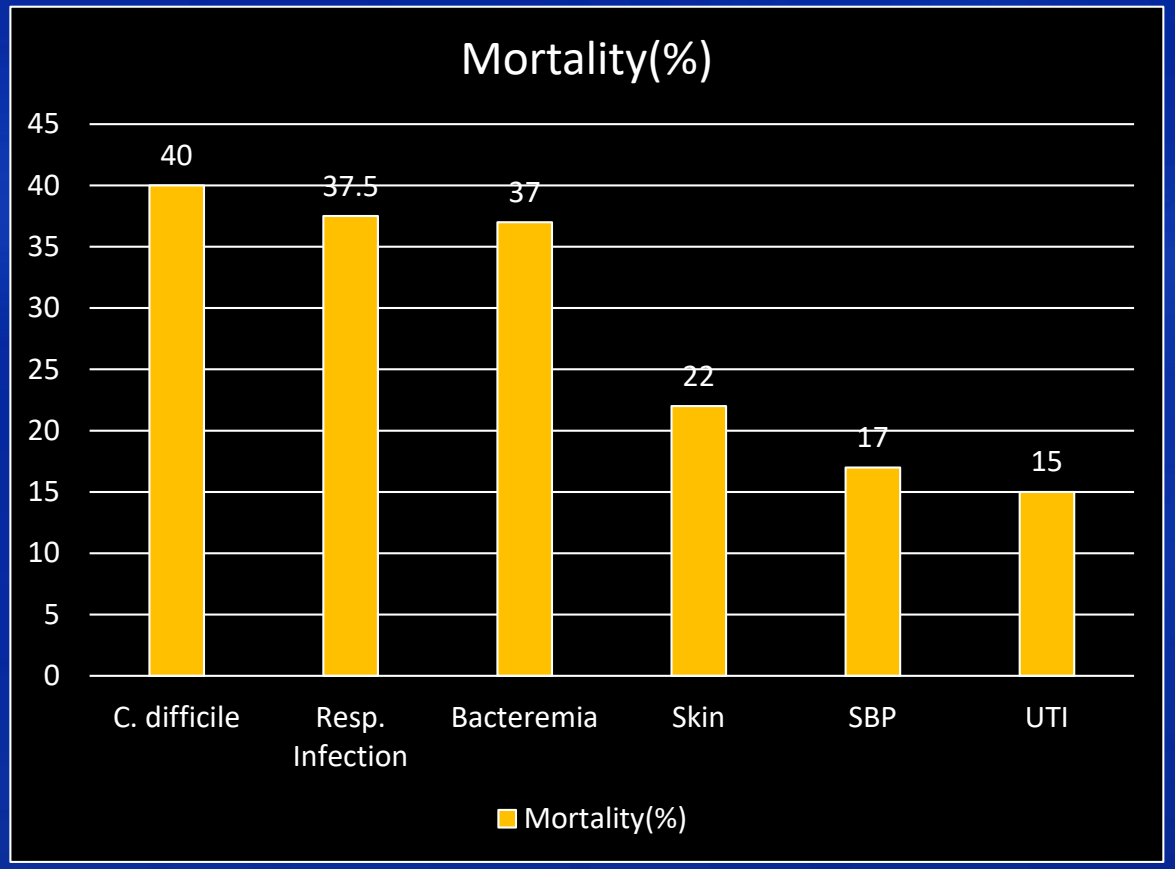
Infections in ACLF

Bajaj JS et al. Hepatology 2012, 56(6): 2328-2335

Pathogen type causing infection in ACLF



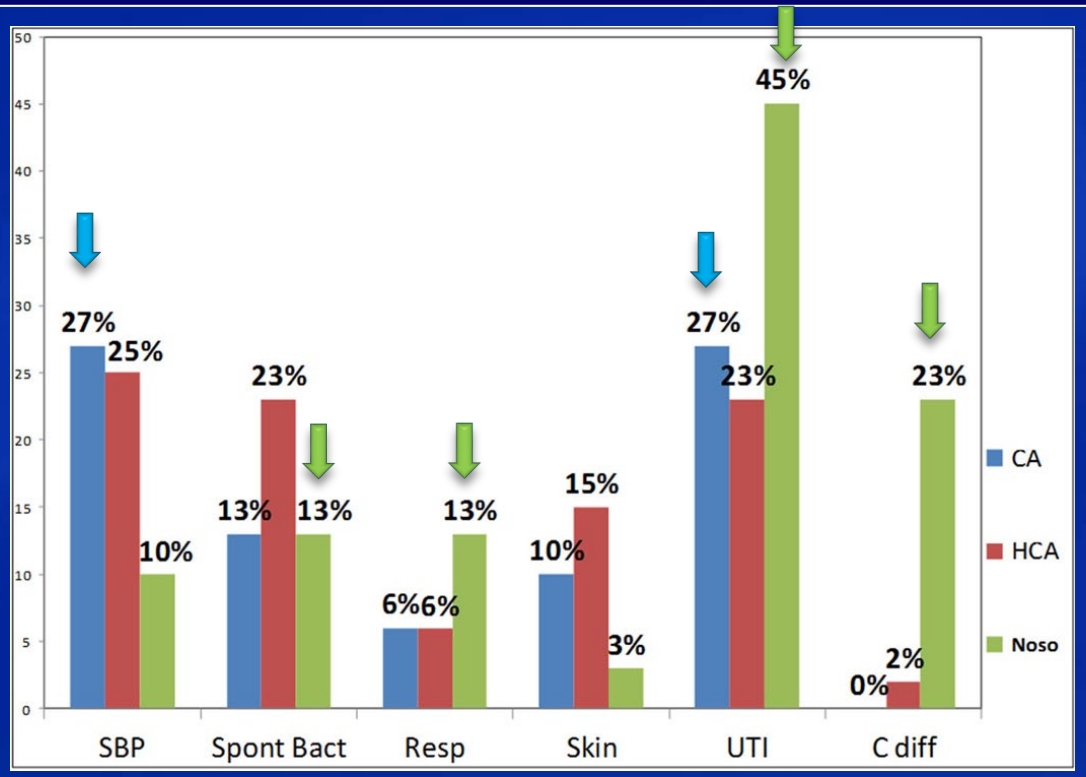
Mortality rate by First Infection



Infections In ACLF

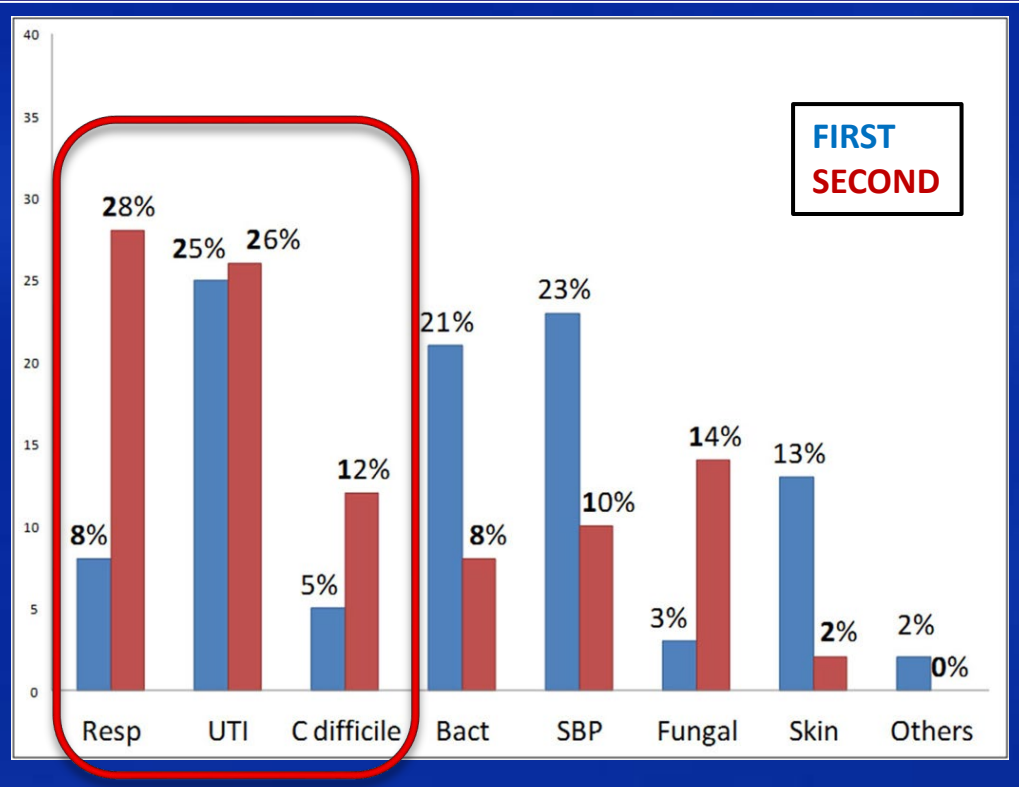
Bajaj JS et al. Hepatology 2012, 56(6): 2328-2335

Acquisition of First Infection by Community-Site & Body Location



-SBP and UTI are the most common **Community Acquired Infections**
-UTI, C difficile, Respiratory and SBP are the most common **First Nosocomial Infections**

First and Second Infection Body Location



Respiratory, UTI, and C diff are the most common **Second Infections** and have very high mortality (OR = 4.4)

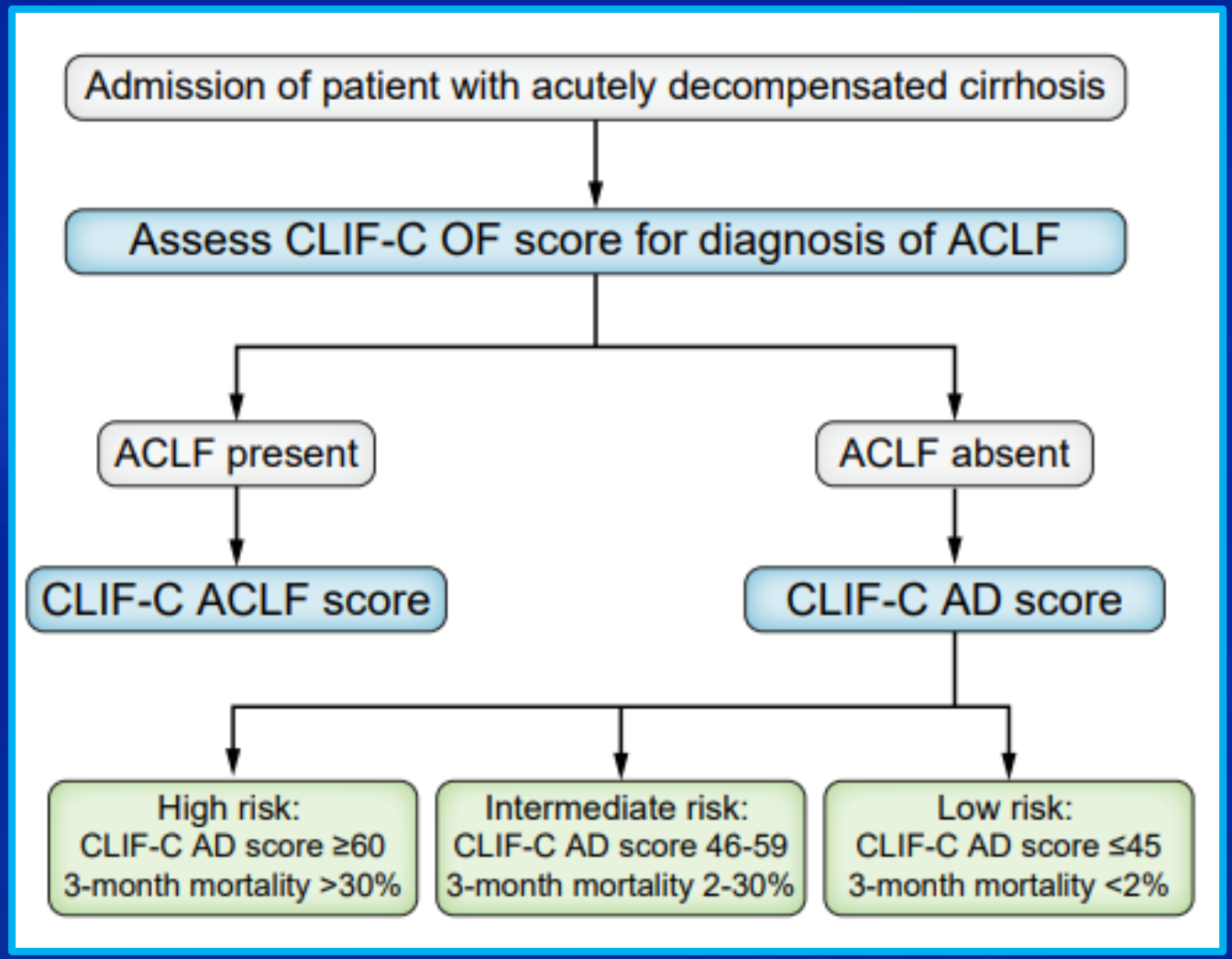
ACLF Evolving Concepts

- Mortality worsens with acquisition of any Nosocomial Infection (> 48 h after admission)
- Windows for therapy:
  - a) Best is before SIRS;
  - b) Before sepsis.
- In HRS, noradrenaline is better tolerated than Terlipressin
- If AKI does nor improve, CRRT is better than SLED.
- Brain edema may occur in Hepatic Encephalopathy of ACLF; need to follow ammonia level to guide therapy.
- In MELD > 30 or refractory HRS-1, MARS or Helios may help as bridge to OLTx.
- Daily Monitoring of ACLF Score helps to assess evolution and response to therapy.

Prevention of ACLF

- Avoid infections, especially nosocomial infections:
  - PPI avoidance (increased risk of SBP & C difficile colitis)
  - Foley catheter avoidance
  - Minimization of duration and optimization of IV-line management
  - Oral care (chlorhexidine) (aspiration pneumonia + Mechanical ventilation)
- Avoid other known triggers of ACLF
  - Proper use of Albumin in LVP
  - Judicious use of antibiotic prophylaxis (d/c in past quinolone resistance)
  - Primary prophylaxis of esophageal variceal bleed.
  - Avoid hepatotoxins
  - Drug minimization
  - PPI avoidance as outpatient
  - Good compliance with drug therapy (AIH, HBV, Wilson)
  - Recognition & management of HBc(+) and HBsAg before immunosuppression

Algorithm of Sequential use of CLIF-C AD score and CLIF-C ACLF score



The CLIF-C Acute-Decompensation Score & Mortality

CLIF-C AD SCORE

CLIF-C AD (Acute Decompensation) score and expected mortality rates

Patients with Acute Decompensation and no ACLF

See score formula

	DATA	CLIF-C AD Score and probability of dying
Age	years	
White-cell count	10^9cells/L	
Creatinine	mg/dl	
INR		
Sodium (Na)	mmol/L	

CLIF-C AD Score	
Probability of dying at 1 month	%
Probability of dying at 3 month	%
Probability of dying at 6 month	%
Probability of dying at 12 month	%

RESET COMPUTE

The CLIF ACLF Grade

CLIF-C ACLF CALCULATOR

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

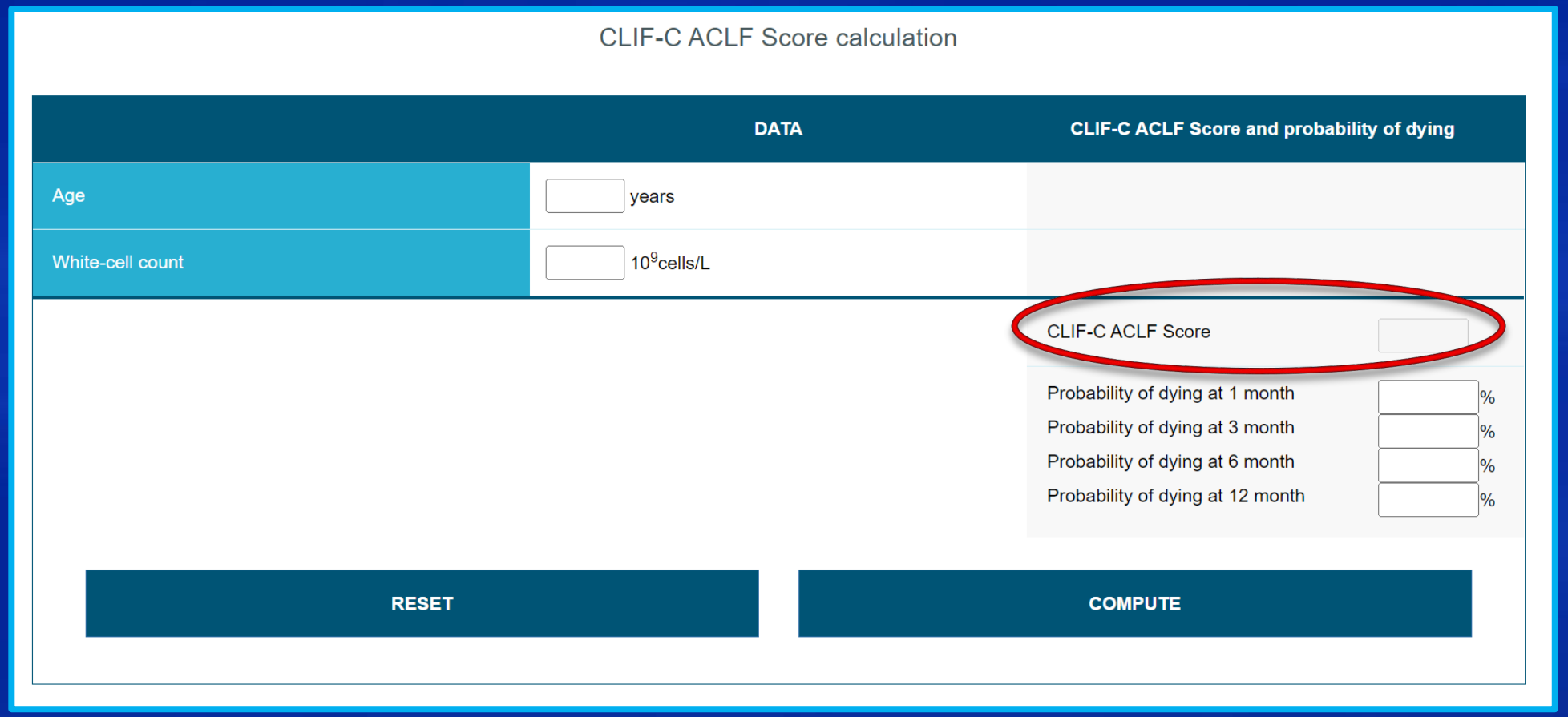
ACLF Grade, CLIF-C OF (Organ Failure) Score and CLIF-C ACLF (ACLF patients) or CLIF-C AD Score (non-ACLF patients with Acute Decompensation)

See score formula

	DATA	CLIF-C Organ Failure Sub-scores
Bilirubin	mg/dl	Liver score Liver failure Yes No
Creatinine	mg/dl	Kidney score Renal failure Yes No
Renal replacement therapy	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	mmHg	Circulatory score Circulatory failure Yes No
Use of vasopressors (Circulatory failure indication)	Yes No	
Select one: PaO_2 (preferred) SpO_2	mmHg %	Lung score Respiratory failure Yes No
FiO_2	%	
Mechanical Ventilation	Yes No	
		Total Number Failures CLIF Organ Failure Score
		ACLF Grade

RESET COMPUTE

The CLIF-C ACLF Score & Mortality



The CLIF Consortium ACLF Score (CLIF-C ACLF)

- CLIF-C ACLF Score = 10 x [0.33 x CLIF-OFs + 0.04 x Age + 0.63 x ln (WBC count) – 2]
- The probability of death (P) at time “t” is:
  - $P = 1 - e[-CI(t) \times \exp(\beta(t) \times \text{CLIF-C ACLFs})]$
- http://www.clifresearch.com/ToolsCalculators.aspx

Algorithm for Management of Acute Decompensation

- Evaluate for evidence of ACLF by using the ***ACLF Calculator***;
- If ACLF, move to ICU for Intensive therapy or Transfer to Transplant Center.
- If no ACLF, then calculate the CLIF-C Acute Decompensation Score.
- ***CLIF-C Acute Decompensation Score*** can assist in management, when ACLF is not present:
  - If </= 45 (< 2% 3-month mortality) consider early discharge;
  - If 46-59 (2-30% 3-month mortality) needs hospital care in ward;
  - If >/= 60 (> 30% 3-month mortality) consider ICU and/or Transplant center transfer due to high risk of progression to ACLF

- http://www.clifresearch.com/ToolsCalculators.aspx

Site of Care, Prognostication, and Futility

Indications for ICU admission

Indications

- Need for organ support (vasopressors, mechanical ventilation, or renal replacement therapy)
- Massive bleeding
- Grade III-IV hepatic encephalopathy (airway protection)
- Septic shock

Contra-indications to ICU admission

- Comorbidities associated with very poor prognosis
- Physiologically and/or biologically elderly patients[a]
- Severe pulmonary (GOLD criteria 3 or 4), cardiac (NYHA functional class III or IV) or neurological disease and ACLF-3
- Advanced neoplasm (life expectancy <6 months)
- Severe frailty[b] secondary to severe sarcopenia (muscle wasting and malnutrition)[c] or a Karnofsky performance status of 40 or less[d]

Time of ICU admission

- Within the first 6 h after diagnosis

Indications for admission at intermediate care structures

- Variceal bleeding
- Grade II-III hepatic encephalopathy
- Sepsis with AKI-HRS or with liver or coagulation failures

Assessment of the risk of death by 30 days

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

Potential rules for stopping organ support

The presence of 4 or more organ failures or a CLIF-C ACLF score >70 points 3-7 days after ICU admission should lead to a re-evaluation of the adequacy of maintaining organ support in the absence of liver transplant options

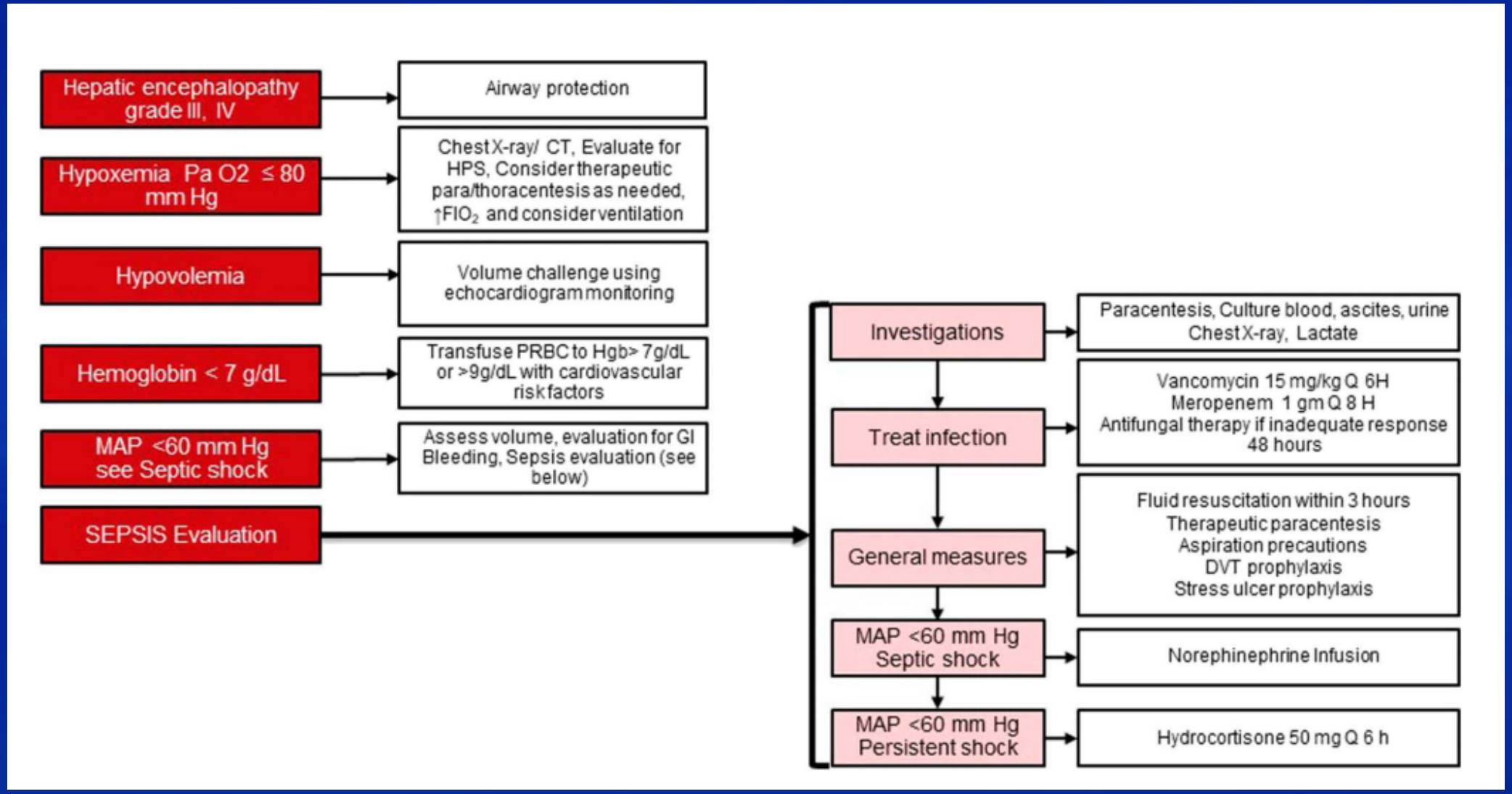
Therapy of ACLF

- Transfer to Transplant Center (if transplant candidate)
- ICU management
- Treat HRS early (monitor urine output and creatinine)
- Monitor Circulatory and Respiratory function.
- Correct intravascular depletion while avoiding excessive fluids.
- Monitor ACLF Score.
- Monitor brain function and ammonia:
  - treat HE,
  - intubate in HE grade III or IV,
  - high suspicion index for brain edema/ Intracranial HTN (ammonia >/=75 mM/L as threshold for cerebral edema).

ICU Management of ACLF

Critical Care Management in ACLF

Bajaj JS et al. Am J Gastroenterol 2022;00:1–28.



ICU Management of ACLF and ALF

Nanchal R et al. Critical Care Medicine March 2020 • Volume 48 • Number 3; e173-191; Bernal, W et al. J Hepatol 75(1): S163-177, 2021

- Use albumin for resuscitation of patients with ALF or ACLF over other fluids (no hydroxyethyl starch nor gelatin solutions) especially when serum albumin is low (< 3 mg/dL).
  - Balanced solutions (D5W 110 mEq/L NaCl + 30 mEq/L Na bicarbonate or LR) are better than 0.9% NaCl (hyperchloremic metabolic acidosis).
- Target to mean arterial pressure of 65 mm Hg in patients with ALF or ACLF, with concomitant assessment of perfusion.
- Place an arterial catheter for blood pressure monitoring in patients with ALF or ACLF and shock.
- Use invasive hemodynamic monitoring to guide therapy in patients with ALF or ACLF and clinically impaired perfusion;
  - CVP or PCWP is not reliable in tense ascites;
  - Do LVP for suspected Intraabdominal HTN.
  - Bedside serial monitoring with Echocardiography can be considered.

ICU Management of ACLF and ALF

Nanchal R et al. Critical Care Medicine March 2020 • Volume 48 • Number 3; e173-191; Bernal, W et al. J Hepatol 75(1): S163-177, 2021

- Use norepinephrine as a first-line vasopressor in patients with ALF or ACLF who remain hypotensive despite fluid resuscitation, or those with profound hypotension and tissue hypoperfusion even if fluid resuscitation is ongoing.
- Add continuous terlipressin (when available) infusion or low-dose vasopressin to norepinephrine in patients with ALF or ACLF who remain hypotensive despite fluid resuscitation to increase blood pressure.
- Use vasopressors, over not using vasopressors, in critically ill patients with ACLF who develop HRS; MAP goal is 85 mm Hg in HRS.

HIGH VERSUS LOW TARGET MEAN ARTERIAL PRESSURE IN MANAGING SEPTIC SHOCK IN CRITICALLY ILL CIRRHOSIS PATIENTS - A PROSPECTIVE OPEN-LABEL RANDOMIZED CONTROLLED TRIAL

- **Objectives:**
  - To assess the efficacy of high (80-85 mm of Hg) versus low (60-65 mm of Hg) in patients with cirrhosis and septic shock in improving 28-day survival
- *Methods:*
  - Open-label single-center randomized controlled trial
  - Patients with cirrhosis and septic shock (n=150)

	Intention-to-treat analysis (n=150)			Per-protocol analysis (n=124)		
	Low MAP (n=75)	High MAP (n=75)	P value	Low MAP (n=67)	High MAP (n=57)	P value
28-day mortality	56%	65%	0.54	60%	61%	0.06
AKI reversal at day 5	31%	45%	0.064	21 (31%)	30 (53%)	0.018
Intradialytic hypotension	25%	8%	0.008	18 (27%)	2 (4%)	<0.001
Length of stay in the intensive care unit	6.2 ± 3.9	7.4 ± 5.2	0.11	6.3 ± 4.0	6.6 ± 4.7	0.71
Reversal of shock at day 5	53%	47%	0.41	40 (53%)	35 (48%)	0.86
Adverse events	11%	24%	0.03			

- Targeting a higher MAP strategy of 80 to 85 compared 60 to 65 mm of Hg in patients with cirrhosis with septic shock is associated with lower incidence of intradialytic hypotension, higher recovery of renal functions but more adverse effects.

Maiwall R, et al. #164

Interpretation of Bedside ECHO IVC to Estimate CVP

Not Validated in Cirrhosis yet

Correlations Between IVC Size and CVP[3]

IVC (cm)	Respiratory Change	CVP (cm H2O)
<1.5	Total collapse	0-5
1.5-2.5	>50% collapse	6-10
1.5-2.5	<50% collapse	11-15
>2.5	<50% collapse	16-20
>2.5	No change	>20

Measure 2cm from IVC/RA junction or 1cm from IVC/hepatic vein junction

ICU Management of ACLF and ALF

Nanchal R et al. Critical Care Medicine March 2020 • Volume 48 • Number 3; e173-191; Bernal, W et al. J Hepatol 75(1): S163-177, 2021
Bajaj JS et al. Am J Gastroenterol 2022;00:1–28.

- In patients with grade 3 or 4 HE, care of the airway by intubation, evaluation of other causes of altered mental status, treatment of potential precipitating factors, and empiric HE therapy should occur simultaneously.
- Consideration for causes other than HE as the reasons for altered mental status is important, especially in patients who have not recovered after HE therapies are deployed.
- Routine use of sedatives is discouraged in patients with grade 3–4 encephalopathy and may be associated with delay in extubating.
- Ventilation in the absence of altered mental status should not be considered brain failure.

ICU Management of ACLF and ALF

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Bajaj JS et al. Am J Gastroenterol 2022;00:1–28.

- In intubated patients, use short-acting dexmedetomidine for sedation as compared to other available agents to shorten time to extubation.
- Use PPI in Ventilated Patients with Cirrhosis but not prophylactic antibiotics.
- The risk of ventilation-associated pneumonia can be decreased by 30- to 45-degree head-end elevation and subglottic suction.
- Use a low tidal volume strategy over high tidal volume strategy in patients with ALF or ACLF and ARDS.
- Recommend against using high PEEP, over low PEEP, in patients with ALF or ACLF and ARDS

ICU Management of ACLF and ALF

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Bajaj JS et al. Am J Gastroenterol 2022;00:1–28.

- Suggest treating porto-pulmonary hypertension with agents approved for pulmonary arterial hypertension in patients with mean pulmonary artery pressure > 35 mm Hg.
- Use supportive care with supplemental oxygen in the treatment of hepato-pulmonary syndrome, pending possible liver transplantation.
- Use high-flow nasal cannula over noninvasive ventilation in hypoxic critically ill patients with ALF or ACLF
- Place chest tube with an attempt to pleurodesis for hepatic hydrothorax in patients in whom TIPS is not an option or as a palliative intent.

ICU Management of ACLF and ALF

Nanchal R et al. Critical Care Medicine March 2020 • Volume 48 • Number 3; e173-191; Bernal, W et al. J Hepatol 75(1): S163-177, 2021
Bajaj JS et al. Am J Gastroenterol 2022;00:1–28.

- Target a serum blood glucose of 110 or 144 to 180 mg/dL in patients with ALF or ACLF.
- Use enteral nutrition over parenteral nutrition in critically ill patients hospitalized with ALF or ACLF without contraindication for enteral feeding.
- Target nutrition with protein goals comparable to critically ill patients without liver failure (20-30 kCal/Kg IBW and 1.2–1.5 ot 2.0 g protein/kg dry or ideal body weight per day). BCAA formulas should not be used routinely.

Therapy of ACLF - Nutrition

- Target for energy is 30–35 kcal/kg/day (or 1-1.4x resting energy expenditure); target for protein is 1.2–1.5 g/kg/day (LoE 4, strong recommendation, strong consensus).
- Restriction of protein intake should be avoided, since it is detrimental in cirrhosis (LoE 2, strong recommendation, strong consensus).
- Oral intake should be preferred whenever possible; if oral intake is not possible, enteral nutrition ideally using a naso-jejunal tube should be attempted. If enteral nutrition is not tolerated, parenteral nutrition can be used as for other critically ill patients (LoE 4, strong recommendation, consensus).

- Micronutrients that should be supplemented if needed include vitamin A, folic acid, thiamine, pyridoxine, vitamin B12, vitamin D, vitamin E, iron, selenium, zinc, calcium, magnesium, phosphorous (LoE 4, strong recommendation, consensus).
- In patients fasting for >12 hours (including nocturnal fasting), intravenous glucose at 2-3 g/kg/day is recommended (LoE 4, weak recommendation, consensus).
- Refeeding syndrome should be monitored, prevented, and treated as early as possible (LoE 4, strong recommendation, strong consensus).
- In patients who experience variceal bleeding/upper gastrointestinal bleeding, oral nutrition should be started as soon as possible. Enteral nutrition can be used safely (LoE 1, strong recommendation, strong consensus)

ICU Management of ACLF and ALF

Nanchal R et al. Critical Care Medicine March 2020 • Volume 48 • Number 3; e173-191; Bernal, W et al. J Hepatol 75(1): S163-177, 2021
Bajaj JS et al. Am J Gastroenterol 2022;00:1–28.

- Use a transfusion threshold of 7 g/dL, over other thresholds, for critically ill patients with ALF or ACLF.
- Use LMWH or vitamin K antagonists, over conservative management, in patients with portal venous thrombosis or pulmonary embolus.
- Use LMWH, over pneumatic compression stockings for VTE prophylaxis in hospitalized patients with ACLF
- Use viscoelastic testing (TEG/ROTEM), over measuring INR, platelet, fibrinogen, in critically ill patients with ALF or ACLF undergoing procedures. In bleeding patients, give 4-Factor Prothrombin Complex (and no FFP) after correction of Fibrinogen to >/= 120 and platelet count.

Use of TEG in Cirrhosis with Clinical Bleeding

Premkumar M et al. Liver Disease, VOL 16, NO 4, OCTOBER 2020

Fibrinogen < 150-200 mg/dL

R-time is in minutes

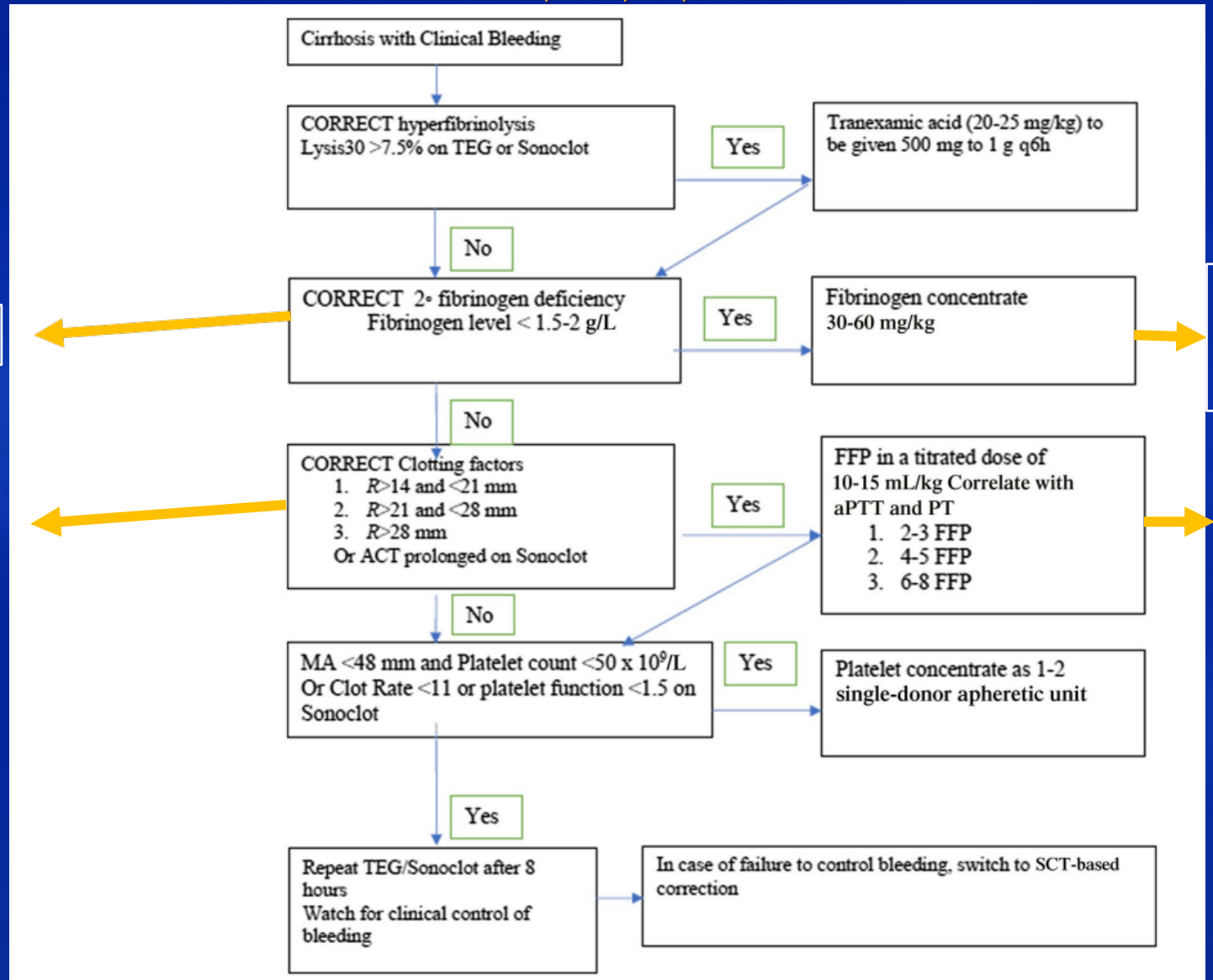

FIG 2 Coagulation correction algorithm using global coagulation tests.

We use Cryoprecipitate. No Fibrinogen Concentrate in USA

Here FFP guided by R-time (minutes) is:
7.5-12 = 1 unit;
12-15 = 2unites;
>15=3 units

ICU Management of ACLF and ALF

Nanchal R et al. Critical Care Medicine March 2020 • Volume 48 • Number 3; e173-191; Bernal, W et al. J Hepatol 75(1): S163-177, 2021
Bajaj JS et al. Am J Gastroenterol 2022;00:1–28.

- Use stress-dose glucocorticoids (hydrocortisone 200 mg/d continuous infusion) in the treatment of septic shock in patients with ALF or ACLF.
- Screen patients with ALF or ACLF for drug-induced causes of liver failure. Drug that are proven or highly suspected to be the cause of ALF or ACLF should be discontinued.
- Adjusting the doses of medications that undergo hepatic metabolism based on the patient's residual hepatic function and using the best available literature. When available, a clinical pharmacist should be consulted.

ICU Management of ACLF and ALF

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Bajaj JS et al. Am J Gastroenterol 2022;00:1–28.

- Assessment for infection because infection is associated with the development of ACLF and increased mortality (moderate quality, strong evidence).
- In patients with cirrhosis and suspected infection, we suggest early treatment with antibiotics to improve survival (very low quality, conditional evidence)
- In patients with cirrhosis and spontaneous bacterial peritonitis (SBP), we recommend albumin in addition to antibiotics to prevent AKI and subsequent organ failures (high quality, strong recommendation).
- In patients with cirrhosis and infections other than SBP, we recommend against albumin to improve renal function or mortality (high quality, strong recommendation).

Therapy of ACLF

- Guided antibiotic use with narrowing of spectrum once sensitivity is known (MDR in 22-38%; Fungal in 2-15%);
  - Treat as MDR in Nosocomial Infections
  - Suspect and Treat for Fungal Infections if not improving in 48 hours
- Intense enteral nutrition (Aspiration risk in PSE)
- Liver Transplantation. if Transplanted:
  - 1-year survival is 75%;
  - high mortality while waiting (overall mortality 50%);
  - mean waiting time: 11 days

Therapy of ACLF

Empirical Antibiotics

- In patients with ACLF and suspected infection, empirical antibiotic treatment should be tailored according to the local epidemiology of bacterial infections and the presence of risk factors for antibiotic resistance (LoE 2, strong recommendation, strong consensus).
- In patients with septic shock or worsening of ACLF, broadspectrum empirical antibiotics covering all potential pathogens should be used (LoE 4, strong recommendation, strong consensus)

Early Empirical Antibiotics and Prognosis

- Patients with ACLF and suspicion of bacterial infections should receive broad-spectrum, empirical antibiotic therapy according to local epidemiology as soon as possible (LoE 3, strong recommendation, consensus).
- In patients with ACLF and suspicion of bacterial infections, rapid and comprehensive infection workup is recommended (LoE 5, strong recommendation, strong consensus).

Therapy of ACLF

Early De-escalation of Empirical Antibiotics

- Early de-escalation of empirical antibiotics (within a 24-to72-hour time frame) should be applied in patients with ACLF receiving broad-spectrum antibiotics. De-escalation should be based on rapid microbiological tests and MDRO colonization data (LoE 5, weak recommendation, con

Empirical Antifungals in ACLF

- Empirical antifungal therapy could be indicated in patients with ACLF developing a nosocomial septic shock who have additional risk factors for fungal infection (LoE 5, weak recommendation, strong consensus).

ICU Management of ACLF and ALF

Nanchal R et al. Critical Care Medicine March 2020 • Volume 48 • Number 3; e173-191; Bernal, W et al. J Hepatol 75(1): S163-177, 2021
Bajaj JS et al. Am J Gastroenterol 2022;00:1–28.

- In hospitalized patients with ACLF because of a bacterial infection who have not responded to antibiotic therapy, we suggest suspicion of an MDR organism or fungal infection to improve detection (very low quality, conditional recommendation).
  - MDR pathogens are reported in 22%–38% of infections in hospitalized patients with cirrhosis, and fungal infections occur in 2-15% of them.
- In patients with cirrhosis, we suggest avoiding PPI unless there is a clear indication, such as symptomatic gastroesophageal reflux or healing of erosive esophagitis, mechanical ventilation, or an ulcer, because PPI use increases the risk of infection (very low quality, conditional recommendation).

ICU Management of ACLF and ALF

Nanchal R et al. Critical Care Medicine March 2020 • Volume 48 • Number 3; e173-191; Bernal, W et al. J Hepatol 75(1): S163-177, 2021
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- In patients with cirrhosis and ACLF who continue to require mechanical ventilation because of adult respiratory distress syndrome or brain-related conditions despite optimal therapy, we suggest against listing for LT to improve mortality (very low evidence, conditional recommendation).

- In patients with end-stage liver disease admitted to the hospital, we suggest early goals of care discussion and if appropriate, referral to palliative care to improve resource utilization.

Therapy of ACLF

HBV Reactivation

- Nucleos(t)ide analogues (NAs) should be started immediately in patients with HBV-related ACLF (LoE 2, strong recommendation, strong consensus).
- In patients with HBV-related ACLF, liver transplantation should be considered in those with a severe presentation (e.g., MELD score >30; ACLF-2 or -3) despite early antiviral treatment initiation, particularly in the absence of early virologic response (< 2-log reduction after 2-weeks) and lack of clinical improvement (LoE 2, strong recommendation, consensus)
- In patients with HBV-related ACLF, the use of NAs reduces mortality (57% vs 15% at 3-months) (LoE 2, strong consensus).

Autoimmune Hepatitis

- In patients with AIH and ACLF, the benefit-risk ratio of the introduction of corticosteroid treatment should be evaluated on a case-by-case basis but corticosteroids should be avoided in case of concomitant uncontrolled infection (LoE 5, strong recommendation, consensus). Child-Pugh > 11 or MELD > 27 predict steroid failure.
- If corticosteroids are administered to patients with AIH and ACLF, close surveillance for infection and strict monitoring of the efficacy of corticosteroid therapy should be performed (LoE 2, strong recommendation, strong consensus). Stop if not improving in day-7.
- Evidence for the role of corticosteroids in patients with AIH and ACLF is very limited (LoE 5, strong consensus).

Therapy of ACLF

Alcoholic Hepatitis and Corticosteroids

- Corticosteroids are not recommended in patients with severe alcohol-related hepatitis and ACLF-3 as only 8.3% respond, nor in patients with uncontrolled bacterial infection (LoE 3, strong recommendation, consensus).
- If corticosteroids are administered to patients with severe alcohol-related hepatitis and ACLF, close surveillance for infection should be performed (LoE 2, strong recommendation, strong consensus).
- With increasing severity of ACLF, corticosteroid responsiveness is progressively reduced whilst the risk of infection increases (LoE 2, strong consensus)

Variceal Bleeding

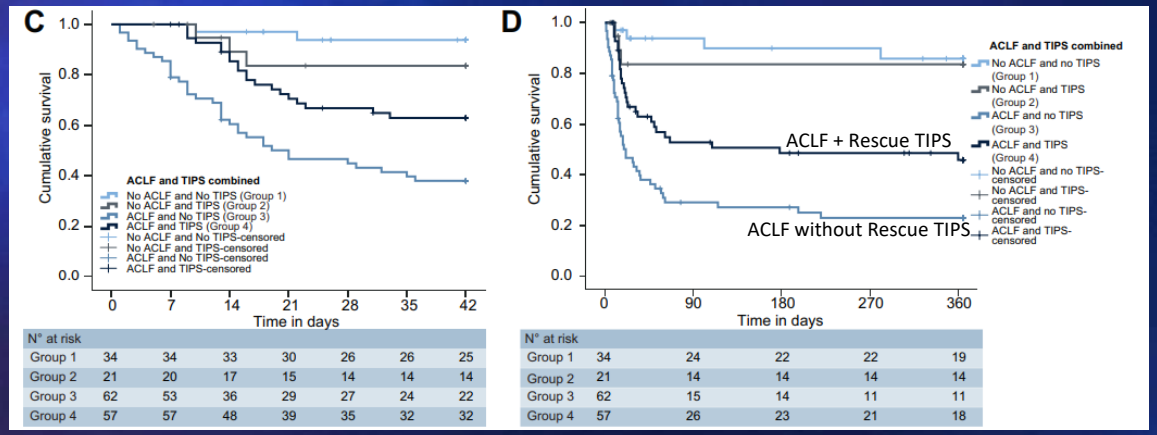
- Both pre-emptive and rescue TIPS should be considered for patients with ACLF and variceal hemorrhage who do not have a contraindication for TIPS (LoE 3, strong recommendation, strong consensus)
- Variceal hemorrhage in patients with ACLF is associated with a very high probability of rebleeding (LoE 3, strong consensus).
- In patients with ACLF, the presence of hepatic encephalopathy should not be considered an absolute contraindication to TIPS (LoE 4, consensus)

TIPS Bridge Therapy for Uncontrolled Bleed

Rescue TIPS Improves Survival in ACLF

1-Year Survival with Rescue TIPS in ACLF

Kumar R et al. Journal of Hepatology 2021 vol. 74: 66–79



N° at risk							
Group 1	34	34	33	30	26	26	25
Group 2	21	20	17	15	14	14	14
Group 3	62	53	36	29	27	24	22
Group 4	57	57	48	39	35	32	32

N° at risk					
Group 1	34	24	22	22	19
Group 2	21	14	14	14	14
Group 3	62	15	14	11	11
Group 4	57	26	23	21	18

6-week Survival with Rescue TIPS by Grade

Walter A et al. Hepatology, VOL. 74, NO. 4: 2085-2101, 2021

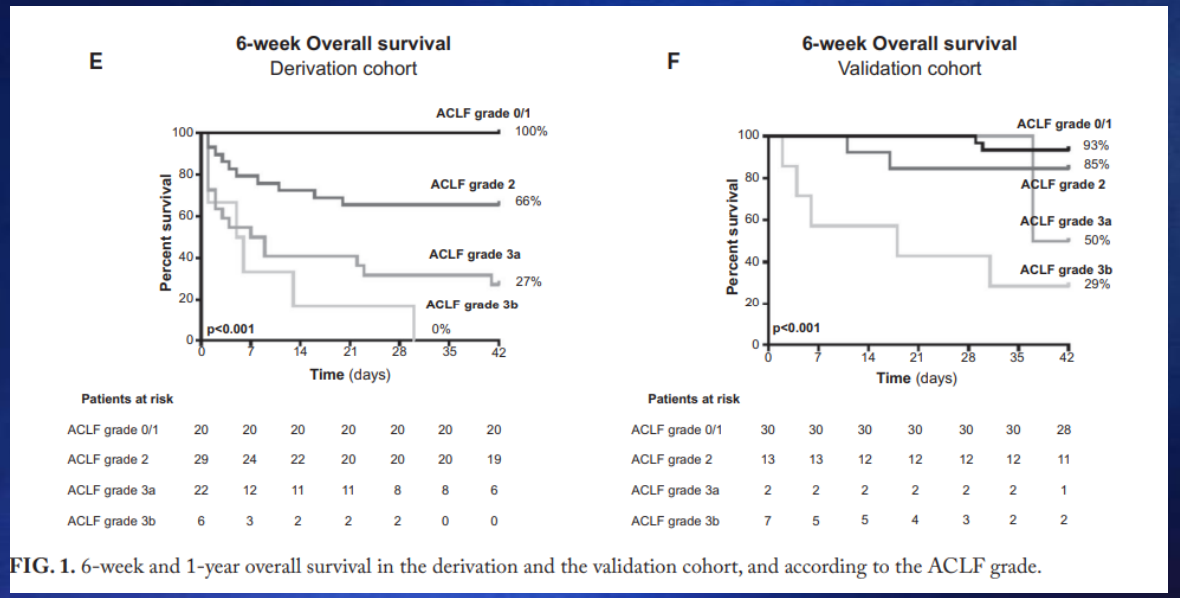


FIG. 1. 6-week and 1-year overall survival in the derivation and the validation cohort, and according to the ACLF grade.

Rescue TIPS Improves Survival in ACLF with up to 3 organ failures

Point of Futility for Rescue / Salvage TIPS

Walter A et al. Hepatology, VOL. 74, NO. 4: 2085-2101, 2021

TIPS is Futile in ACLF with >/= 4 Organ Failures (3b)

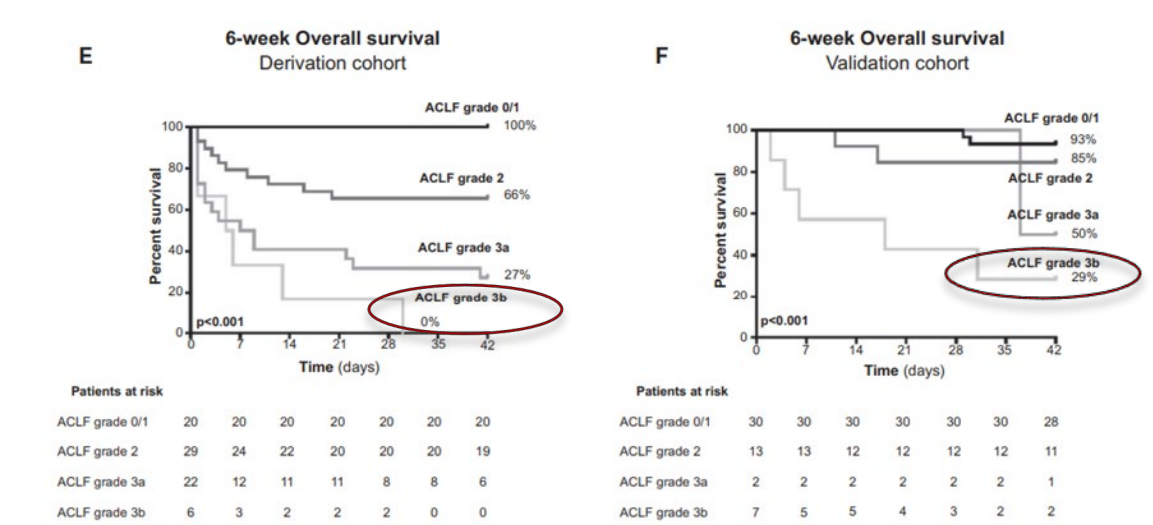


FIG. 1. 6-week and 1-year overall survival in the derivation and the validation cohort, and according to the ACLF grade.

TIPS is Futile if Lactate is >/= 12 mmol/L or MELD >/= 30

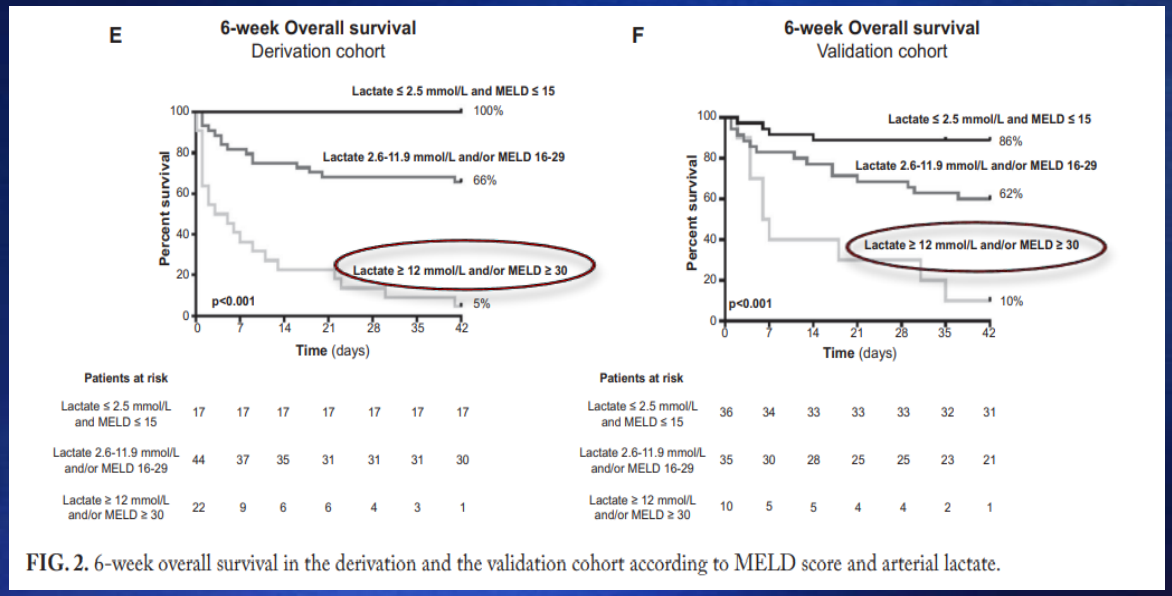


FIG. 2. 6-week overall survival in the derivation and the validation cohort according to MELD score and arterial lactate.

Therapy of ACLF – Less Established

- G-CSF for selected patients:
  - Not studied in patients with sepsis, multiorgan failure nor HE III or IV
  - Usually given as soon as ACLF-2 is reached or if Bili >/= 12 mg/dL.
- Plasma Exchange
- Selective use of MARS/Prometheus (as bridge to Liver Tx)
  - Does not improve survival over standard medical therapy (Br J Surg. 2011 May;98(5):623-31)

g-CSG in ACLF

g-CSF Use

(Shiv Kumar Sarin)

- Contraindications for g-CSF
  - Sepsis, severe sarcopenia, severe anemia; AKI?
  - Macrophage activation syndrome
  - Ferritin > 1000 ng/mL, high LDH, skin with “slate gray color”
  - Plasmapheresis

- Predicting good response to g-CSG
  - BM Bx with:
    - high osteoblasts,
    - high CD34,
    - low vascularity,
    - low perivascular fibrosis,
    - high Hematopoietic Stem Cells (HSC), Multi Potential Progenitors (MPP), and Common Myeloid Progenitors (CMP).

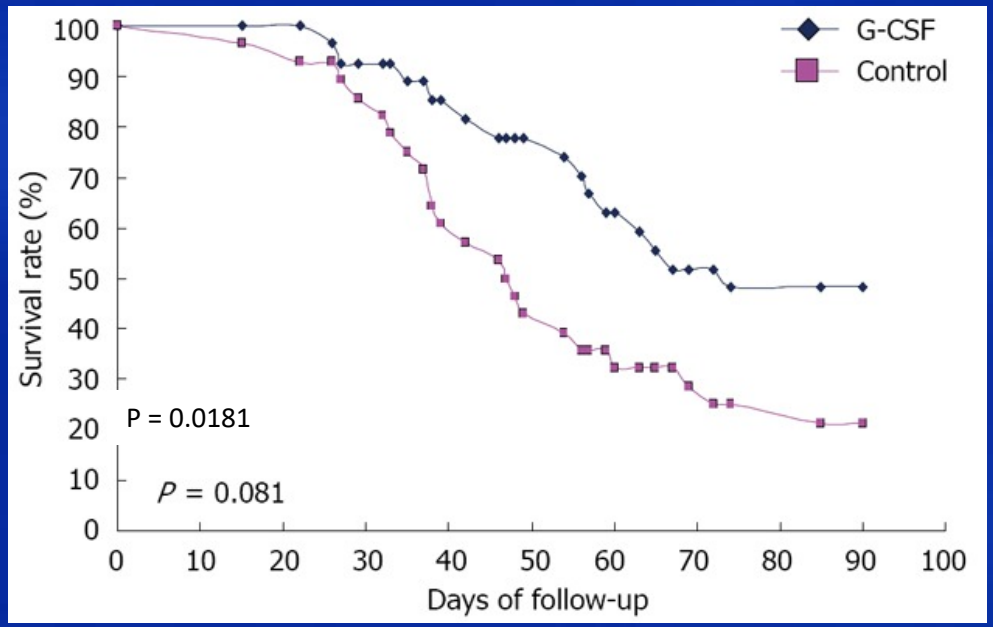
Granulocyte-colony stimulating factor therapy improves survival in patients with hepatitis B virus-associated acute-on-chronic liver failure

Duan XZ et al. World J Gastroenterol 2013 Feb 21;19(7):1104-10

g-csf 5 mcg/kg/d SQ x 6 days vs Placebo (+ Entecavir in all)

Parameters	G-CSF group (27)	Control group (28)	*P* value
Gender (male %)	22 (81.5)	22 (78.6)	0.755
Age (yr)	43.5 (29-63)	45.9 (22-65)	0.332
WBC (10^9/L)	5.79 ± 1.81	6.61 ± 1.71	0.443
Neutrophil (10^9/L)	3.53 ± 1.46	3.82 ± 1.17	0.114
Platelets (10^9/L)	182 (147-215)	174 (149-175)	0.680
ALT (U/L)	276 (197-801)	252 (189-1239)	0.430
AST (U/L)	246 (195-788)	251 (187-980)	0.544
Total bilirubin (mg/dL)	20 (11-30)	19 (10.5-30)	0.605
Cr (mg/dL)	1 ± 0.2	1 ± 0.6	0.475
INR	2.11 ± 0.28	2.34 ± 0.34	0.606
ALB (g/L)	29.11 ± 4.05	28.75 ± 4.63	0.596
HBV DNA ($\log_{10}$)	5.11 ± 1.37	5.55 ± 1.59	0.280
CTP score	12.17 ± 1.47	12.25 ± 1.29	0.349
MELD score	25.11 ± 3.30	26.30 ± 4.12	0.588

SURVIVAL



G-CSF therapy promoted CD34(+) cell mobilization in patients with HBV-associated ACLF, and improved the liver function and the survival rate of these patients.

Granulocyte colony-stimulating factor mobilizes CD34(+) cells and improves survival of patients with acute-on-chronic liver failure

Garg V et al Gastroenterology 2012 Mar;142(3):505-512

Parameters	Group A (n = 23)	Group B (n = 24)	*P* value
Male/female	20/3	21/3	.71
Age (*y*)	40 (30–65)	40 (19–55)	.70
Ascites	23 (100)	24 (100)	1
Total leukocyte count ($\times 10^3/mm^3$)	10.7 (3.9–22.1)	11.8 (3.8–28.7)	.34
Creatinine (*mg/dL*)	0.8 (0.5–3.7)	1.0 (0.3–4.9)	.06
Bilirubin (*mg/dL*)	25.6 (9.0–43.5)	23.9 (6.2–36.1)	.53
INR	2.20 (1.66–3.92)	2.71 (1.70–4.53)	.12
Encephalopathy	5 (10.6)	8 (17)	.51
Grade of encephalopathy	2 (1–2)	2 (1–2)	.28
Grade of varix (n = 42)	2 (0–3) (n = 22)	2 (0–4) (n = 20)	.32
Grade of varices ≥2	15 (65.2)	17 (70.8)	.76
Hepatorenal syndrome	4 (8.5)	5 (10.6)	1
HBV DNA $\log_{10}$ (*IU/mL*) (n = 11)	5.34 (5.04–6.60) (n = 4)	5.50 (4.76–7.93) (n = 7)	.91
HVPG (*mm Hg*) (n = 21)	16 (13–28) (n = 11)	19.25 (11–30) (n = 10)	.32
Fibrosis score (modified Ishak) (n = 18)	4 (0–5) (n = 10)	4 (0–4) (n = 8)	.237
CTP score	12 (11–14)	12 (10–14)	.91
MELD score	29 (21–40)	31.5 (20–40)	.069
SOFA score	5 (4–9)	6 (4–10)	.40

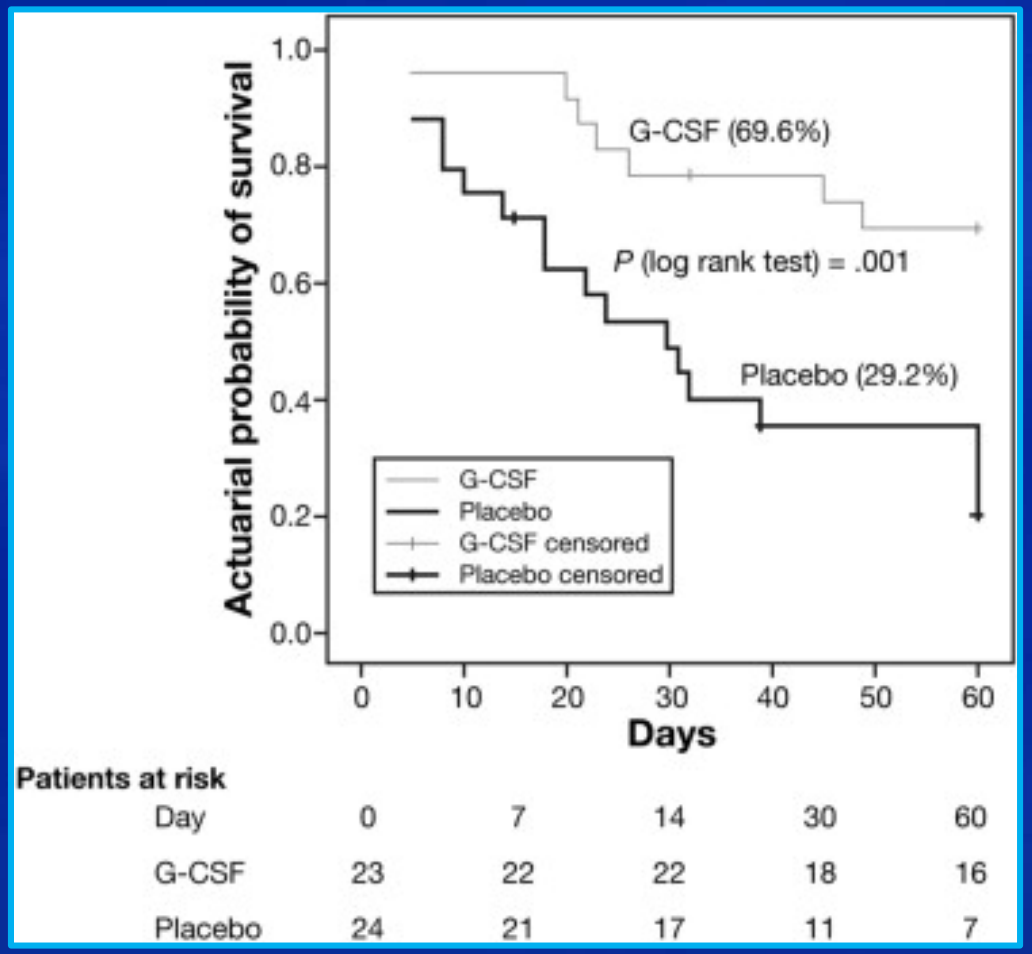
Acute event	Group A	Group B
Alcoholic hepatitis	15 (65)	12 (50)
Reactivation of hepatitis B virus	4 (17)	6 (25)
Antitubercular therapy	2 (9)	1 (4)
Hepatitis E virus infection	1 (4)	2 (8)
Cryptogenic	1 (4)	3 (12)
Underlying chronic liver disease		
Alcoholic liver disease	17 (74)	12 (50)
Hepatitis B	4 (17)	7 (30)
Cryptogenic	2 (9)	4 (16)

Granulocyte colony-stimulating factor mobilizes CD34(+) cells and improves survival of patients with acute-on-chronic liver failure

Garg V et al Gastroenterology 2012 Mar;142(3):505-512

Survival

[g-csf 5 mcg/kg/d x 5 d; then q 3rd d x 7 more doses] vs [Placebo]



Patients at risk

Day	0	7	14	30	60
G-CSF	23	22	22	18	16
Placebo	24	21	17	11	7

Considerations + Conclusion

- Patients with HCC or sepsis were excluded.
- **The percentages of patients who developed hepatorenal syndrome, hepatic encephalopathy, or sepsis were lower in the g-csf group than in the placebo group (19% vs 71% [*P* = .0002], 19% vs 66% [*P* = .001], and 14% vs 41% [*P* = .04], respectively**
- **Survival was higher in the g-csf group (69.6 %) than in the placebo group (29.2%)**

Granulocyte Colony-Stimulating Factor in Severe Alcoholic Hepatitis: A Randomized Pilot Study

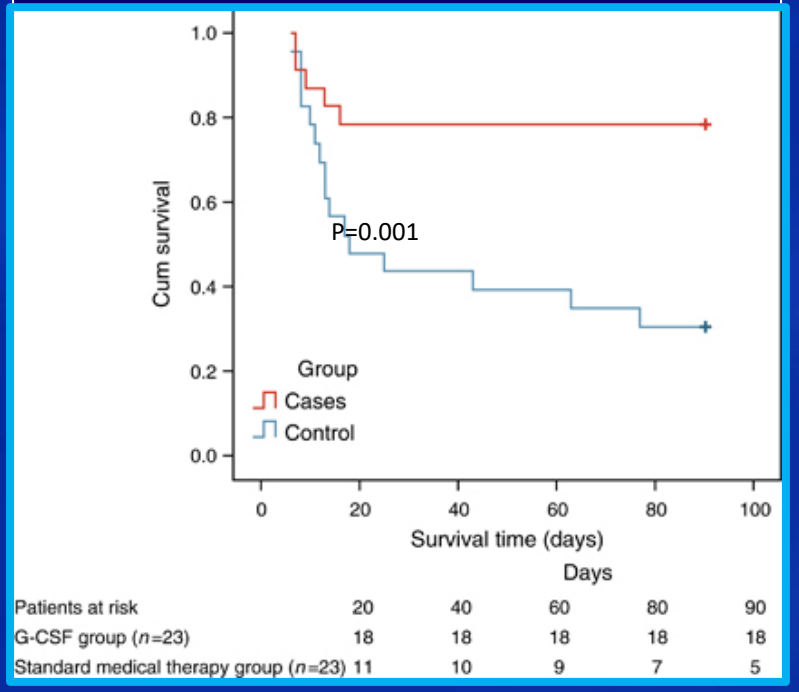
Singh V et al. Am J Gastroenterol 2014 Sep;109(9):1417-23

g-csf 5 mcg/kg BID SQ x 5 d vs Placebo
(All had Pentoxifylline 400 TID + Nutrition)

Variables	Group A (G-CSF; *n*=23)	Group B (SMT; *n*=23)	*P* value
Age (years)	41.7±7.5	44.3±13	0.417
Sex (M/F)	23:0	23:0	
Duration of symptoms before admission (days)	13.6±5.3	16.1±8.4	0.395
Total leukocyte count (/mm^3)	13,735±8,680	17,830±9,770	0.140
Platelets (/mm^3)	143,050±74,500	171,430±77,280	0.211
Bilirubin (mg/dl)	20.1±11.5	20.0±11.4	0.994
Alanine aminotransferase (IU/l)	101±41	136±95	0.118
Alkaline phosphatase (IU/l)	124±50	137±73	0.484
Albumin (g/dl)	3.0±0.7	2.8±0.5	0.437
Prothrombin time (s)	31.1±14	27.9±7.2	0.33
International normalized ratio	2.5±1.2	2.3±0.9	0.523
Sodium (mEq/dl)	135±8	135±9	0.762
Serum creatinine (mg/dl)	1.04±0.50	1.25±0.41	0.138
CTP score*	12	12	0.403
mDF score*	85.5	79.2	0.398
MELD score*	27	30	0.538
CD34$^+$ cells	0.31±0.45	0.15±0.2	0.51

Excluded HCC, uncontrolled infection, Portal V. thrombosis, previous corticosteroid use.

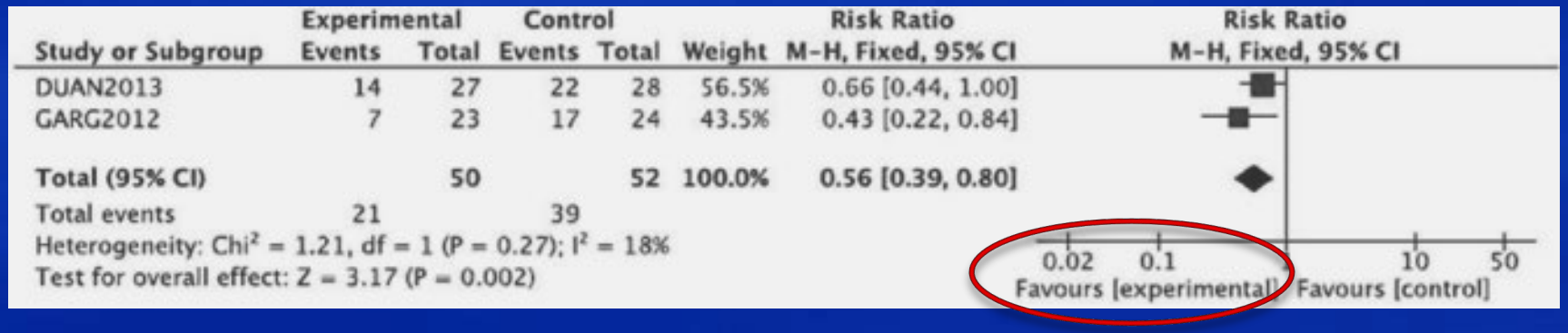
Survival + Conclusion



G-CSF is safe and effective in the mobilization of hematopoietic stem cells and improves liver function as well as survival in patients with severe alcoholic hepatitis

Granulocytecolony stimulating factor for acute-on-chronic liver failure: systematic review and meta-analysis of randomized control trials

Chavez-Tapia NC et al Annals of Hepatology Volume 14, Issue 5, September–October 2015



Plasma Exchange in ACLF

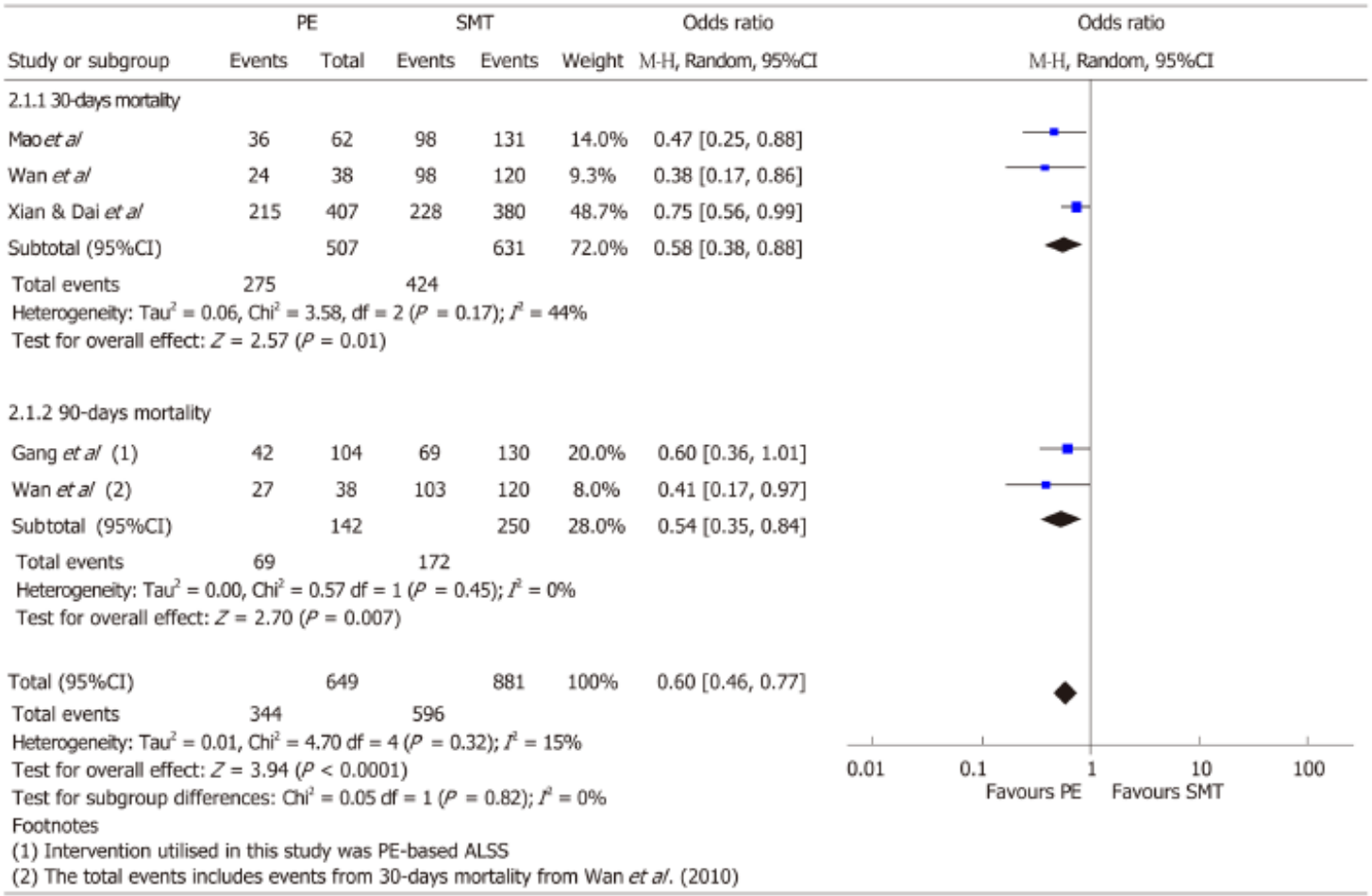
Plasma Exchange in ACLF: Systematic Review

Tan EX et al. World J Gastroenterol 2020 January 14; 26(2): 219-245

- Most studies in ACLF were in patients with chronic HBV reactivation. Many of them were not cirrhotic.
- Plasma exchange of FFP 40-60 mL/kg +/- 5% Albumin at 20-30 mL per minute, 2 to 3 times a week x 3 sessions.
- There was survival improvement in non-transplanted patients.
- Is unclear if this data can be extrapolated to other populations; prospective studies are needed.

Plasma Exchange in ACLF: Systematic Review

Tan EX et al. World J Gastroenterol 2020 January 14; 26(2): 219-245



Study or subgroup	PE Events	PE Total	SMT Events	SMT Events	Weight	Odds ratio M-H, Random, 95%CI
2.1.1 30-days mortality						
Mao *et al*	36	62	98	131	14.0%	0.47 [0.25, 0.88]
Wan *et al*	24	38	98	120	9.3%	0.38 [0.17, 0.86]
Xian & Dai *et al*	215	407	228	380	48.7%	0.75 [0.56, 0.99]
Subtotal (95%CI)		507		631	72.0%	0.58 [0.38, 0.88]
Total events	275		424			
Heterogeneity: $Tau^2 = 0.06$, $Chi^2 = 3.58$, df = 2 ($P = 0.17$); $I^2 = 44\%$						
Test for overall effect: $Z = 2.57$ ($P = 0.01$)						
2.1.2 90-days mortality						
Gang *et al* (1)	42	104	69	130	20.0%	0.60 [0.36, 1.01]
Wan *et al* (2)	27	38	103	120	8.0%	0.41 [0.17, 0.97]
Subtotal (95%CI)		142		250	28.0%	0.54 [0.35, 0.84]
Total events	69		172			
Heterogeneity: $Tau^2 = 0.00$, $Chi^2 = 0.57$ df = 1 ($P = 0.45$); $I^2 = 0\%$						
Test for overall effect: $Z = 2.70$ ($P = 0.007$)						
Total (95%CI)		649		881	100%	0.60 [0.46, 0.77]
Total events	344		596			
Heterogeneity: $Tau^2 = 0.01$, $Chi^2 = 4.70$ df = 4 ($P = 0.32$); $I^2 = 15\%$						
Test for overall effect: $Z = 3.94$ ($P < 0.0001$)						
Test for subgroup differences: $Chi^2 = 0.05$ df = 1 ($P = 0.82$); $I^2 = 0\%$						

Footnotes
(1) Intervention utilised in this study was PE-based ALSS
(2) The total events includes events from 30-days mortality from Wan *et al*. (2010)

Figure 2 Forest plot for 30- and 90- d mortality in acute-on-chronic liver patients undergoing plasma exchange-based interventions or standard medical treatment. PE: Plasma exchange; SMT: Standard medical treatment.

Liver Transplant in ACLF

Therapy of ACLF – Liver Transplant

Liver Transplant in ACLF

- An early assessment for liver transplantation should be proposed for all patients with severe ACLF (ACLF-2 or -3) (LoE 2, strong recommendation, strong consensus)
- Liver transplantation is associated with a clear survival benefit in patients with severe ACLF, but the limits of patient suitability are unknown (LoE 2, strong consensus).
- Liver transplantation of patients with severe ACLF is associated with a substantial increase in resource utilization (LoE 3, strong consensus)
- Delaying liver transplantation for patients with severe ACLF (ACLF-2 or -3) increases the risk of waitlist and posttransplant mortality (LoE 3, strong consensus)

Futility of Liver Transplant

- The futility of liver transplantation of patients with ACLF-3 should be decided on a case-by-case basis considering independent predictors of post-transplantation mortality (LoE 5, strong recommendation, strong consensus)
- Defining criteria for futile liver transplantation in patients with ACLF-3 is an urgent medical need (n.a., strong consensus).

Risk factors could be used to define limits of transplantation, including severe frailty (defined by a clinical frailty scale >−7), ongoing sepsis except for urinary tract infections, previous infection with pan-drug resistant bacteria, a respiratory failure with PaO2/FiO2 ratio 1 lg/kg/min, arterial lactate >9 mmol/L and worsening clinical course.

Therapy of ACLF – Liver Transplant

Extended Criteria Organs	Living Donors
• Extended criteria donor livers should be considered for listed patients with ACLF-3 to reduce mortality on the waiting list (LoE 4, strong recommendation, consensus).	• Living donor liver transplantation should be considered for patients with ACLF-3 in experienced centres (LoE 2, strong recommendation, consensus).

Liver Transplant and Futility

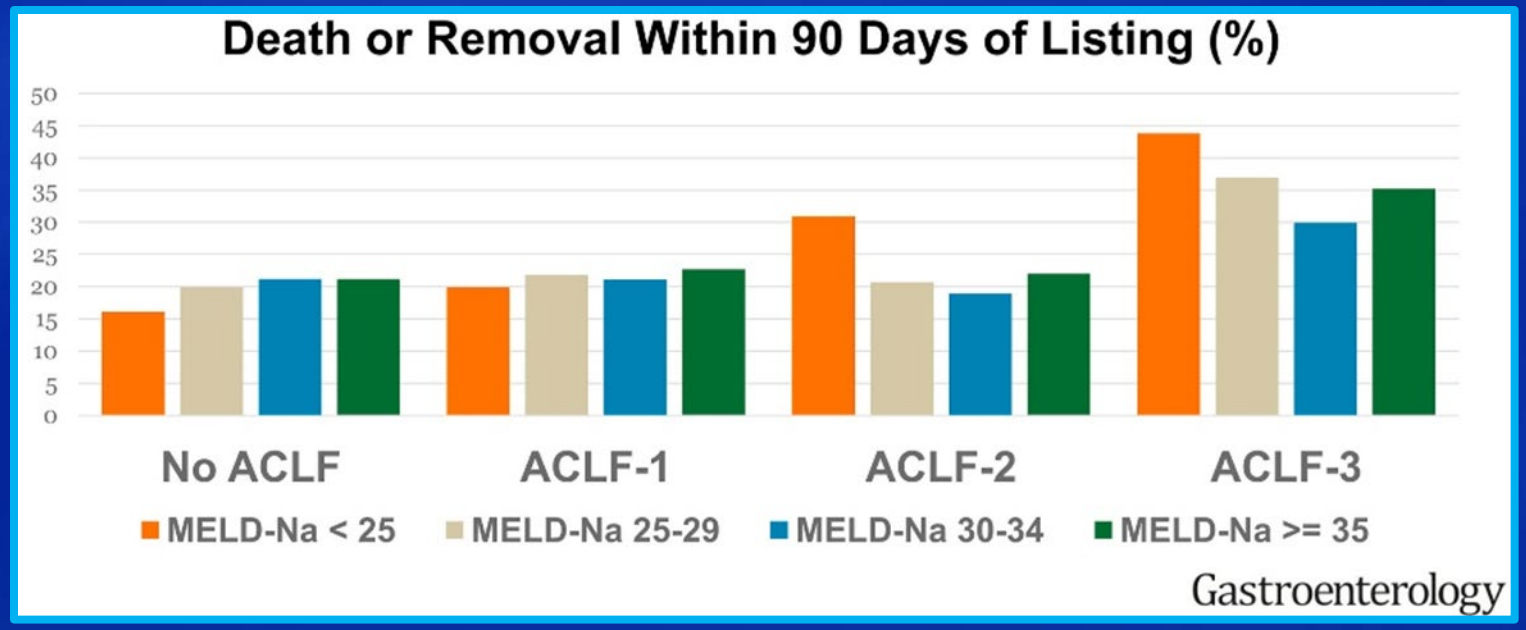
- Liver Transplant has a 1-year survival of 70 to 84%. Patients with more organ failures have lower survival (4 or more OF 80%, 3 OF: 43-84%; 2 OF: 72-88%). Respiratory failure gives lower survival.
  - Decision to move to Transplant should be done in the first 3-7 days
  - ACLF score should be re-calculated daily, if transplant listed.
    - Patients who improve from ACLF-3 to lower degree are good transplant candidates.
  - Respiratory failure is a contraindication.
- In case of contraindication of LT, the presence of ≥4 OFs or a CLIF-C ACLF score >70 at days 3 to 7 after diagnosis could indicate the futility of care.

Effect of ACLF Grade and MELD in 90-day Removal or Death after Listing for Liver Transplant

Sundaram , V et al Gastroenterology 2019, 156 :1381-1391

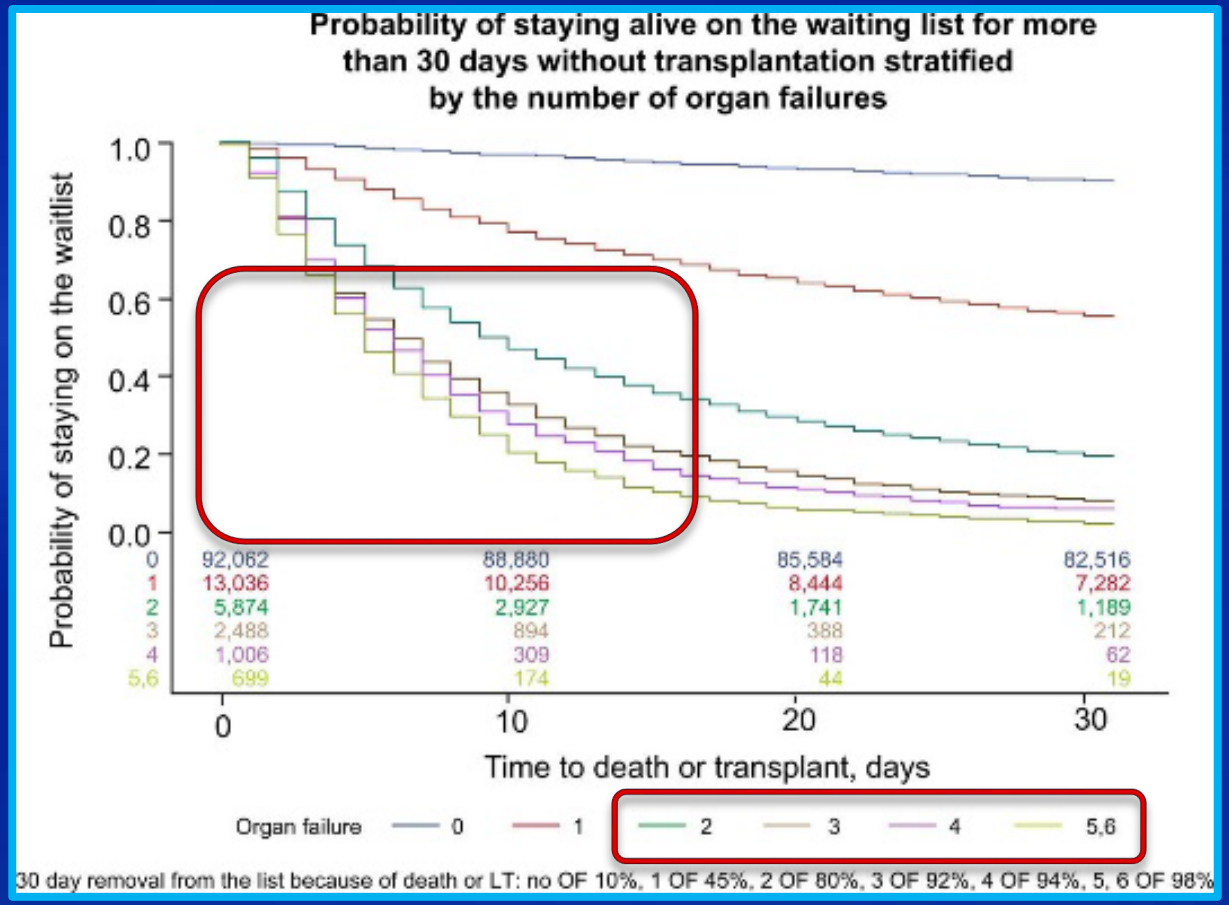
Patients with ACLF-3 have poor outcomes regardless of MELD-Na score.

Liver transplantation increases odds of survival for these patients, particularly if performed within 30 days of placement on the waitlist



Probability of Survival after Liver Transplant Listing in ACLF (UNOS 2002-2016)
Effect of Number of Organ-Failures

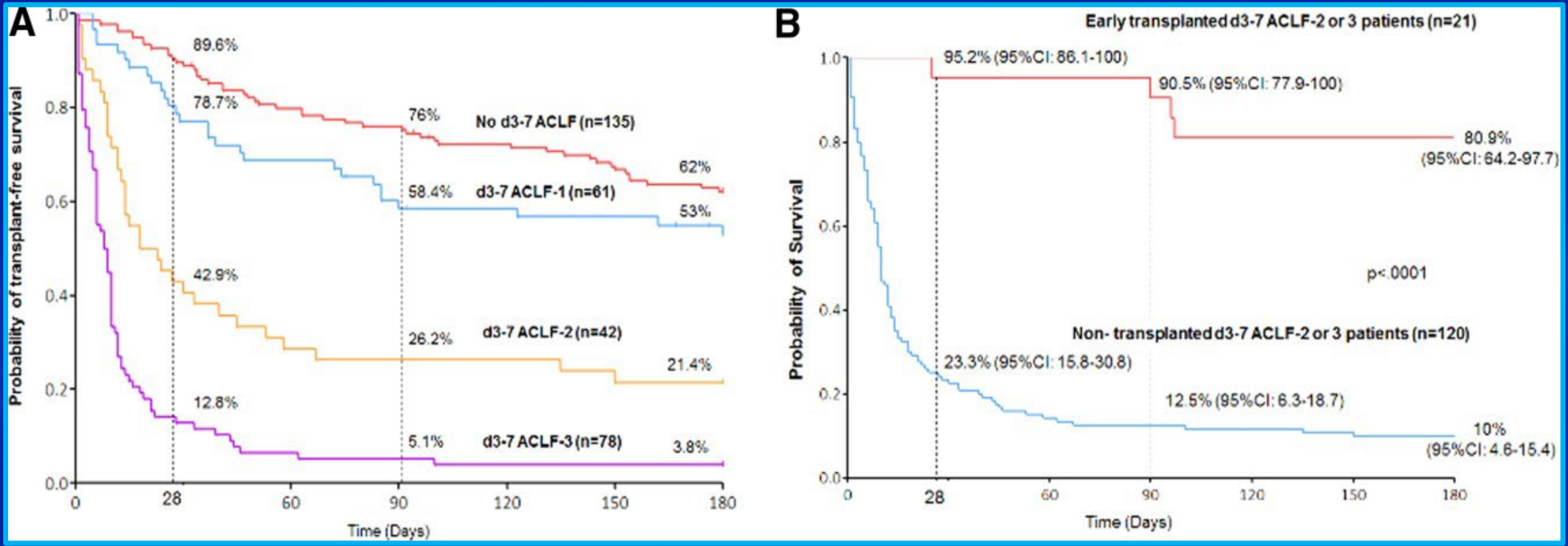
Thuluvath, P et al J Hepatol. 2018 Nov;69(5):1047-1056



Window for Transplantation is very short with >/= 2 OFs. Early listing is needed.

Mortality by Grade of ACLF by days 3-7 after Diagnosis

Gustot T et al. Hepatology. 2015 Jul;62(1):243-52



Early LTx 1-year Survival = 75%
Reasonable for ACLF-1 or 2
ACLF-3 do poorly

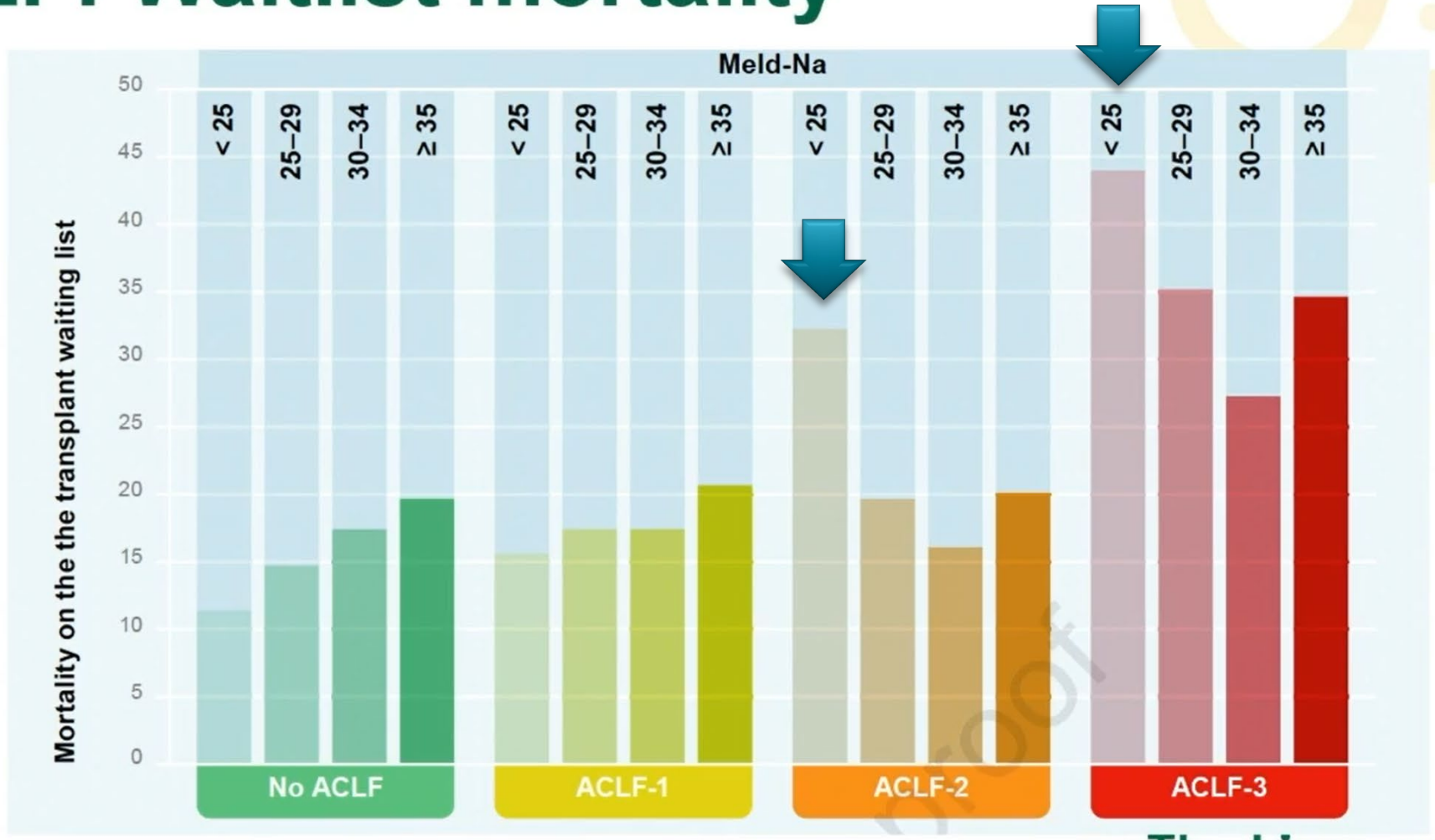
Exclusions & Complications for Liver Tx in ACLF

Artru, F et al. J Hepatol. 2017; 67:708–715

- Exclusions:
  - Active bleeding
  - Sepsis controlled < 24 hours
  - Noradrenaline > 3 mg/hour
  - Severe ARDS
- Complications:
  - Vascular (27.4%
  - Biliary (27.4%)
  - Infection (80% Bacterial; 15% Fungal)

- Survival at 1-year:
  - No ACLF 90%
  - ACLF-1: 82.3%
  - ACLF-2: 86.2%
  - ACLF-3: 82.6%

ACLF: Waitlist mortality



Jalan R et al. J Hepatol. 2021 Jun 23;S0168-8278(21)00437-2.

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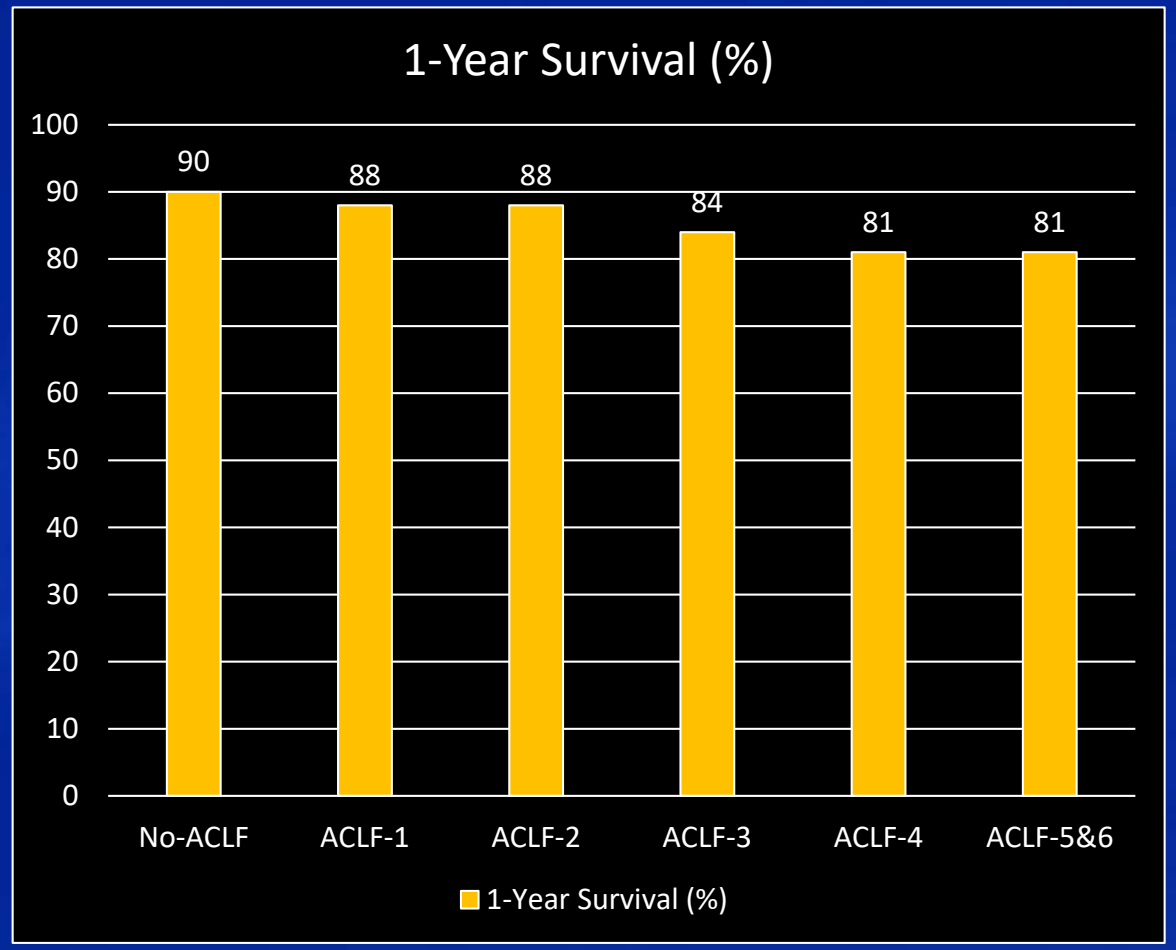
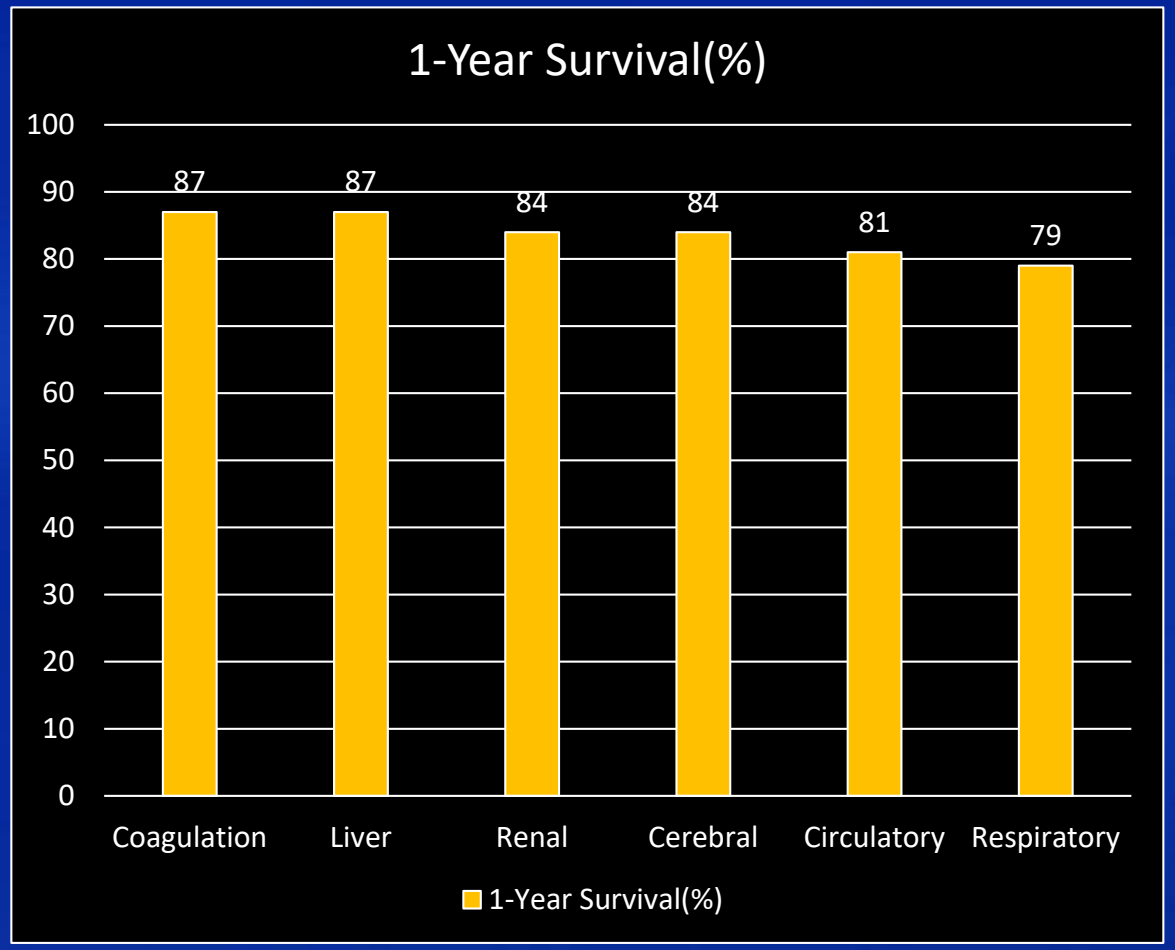
Registry Data of Liver Tx in ACLF; 1-Year Survival

Thuluvath, P et al J Hepatol. 2018 Nov;69(5):1047-1056





Factors Affecting 1-Year Survival after OLTx in ACLF-3

Sundaram , V et al Gastroenterology 2019, 156 :1381-1391

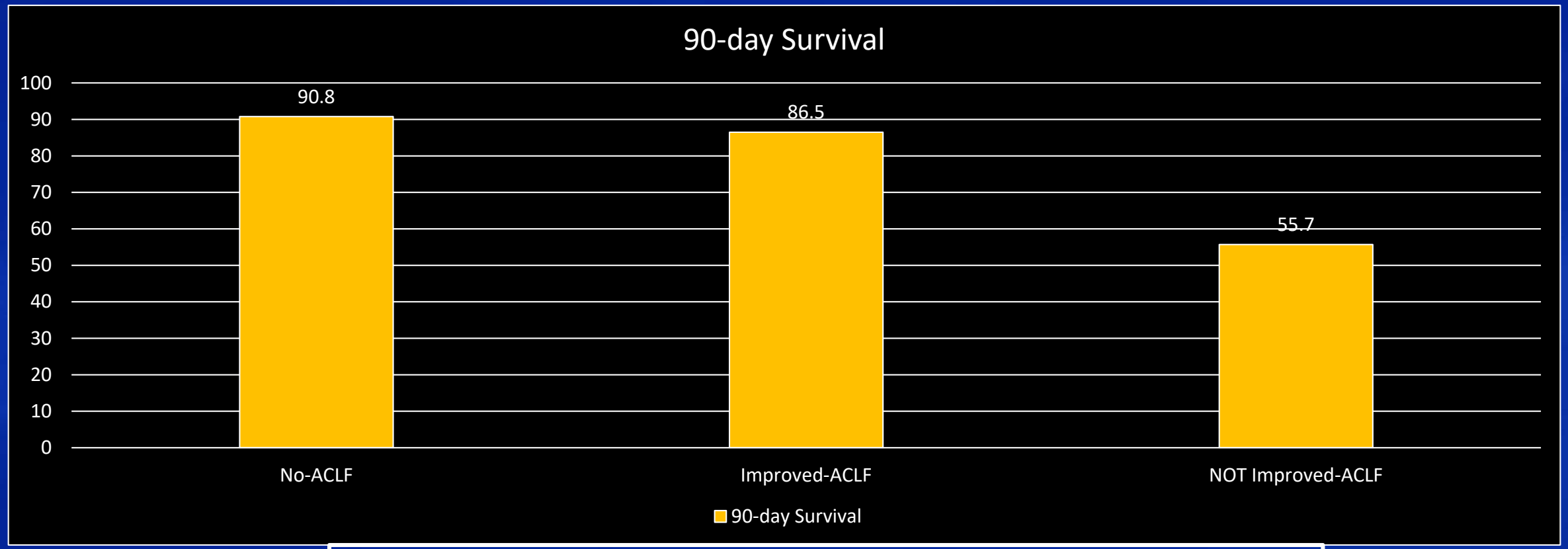
Variable	YES	NO
Mechanical Ventilation	0.753	0.854
DRI >/= 1.7	0.781	0.829
No Liver Tx within 30-days of Listing	0.781	0.825

Patients have worse survival with:
-Mechanical Ventilation (75% vs 85%),
-Poor graft Quality (71% vs 76%), or
-Transplanted after 30 days (73% vs 76%)

Transplantation within the initial 14 day has big impact in ACLF-4 (80.9 vs 75.8%) and ACLF-5 (79.3 vs 67.2%)

Effect of ACLF Improvement in 90-day LTx Outcome

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



Clinical improvement was defined as restoration of at least one previously failed organ system between the diagnosis of ACLF and OLT

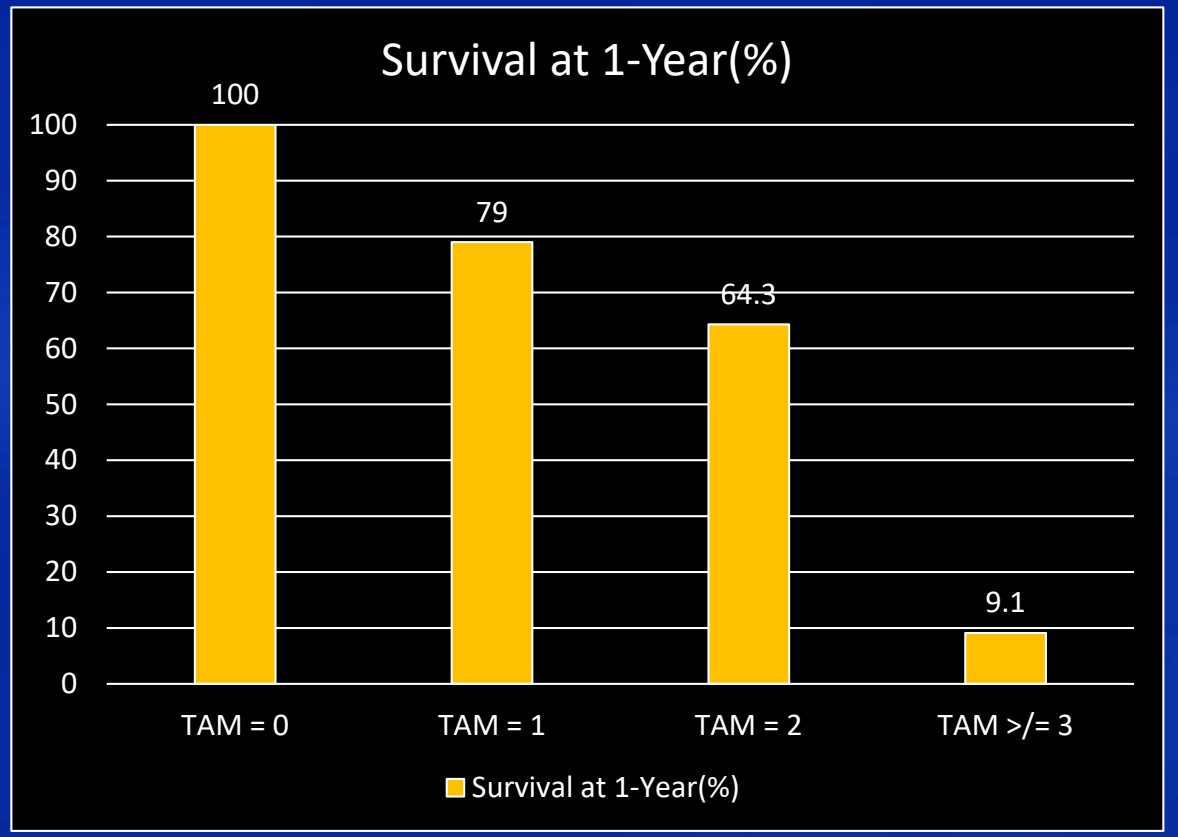
Best impact is from Resolution of Respiratory Failure, or Brain Failure, or Circulatory Failure

Sundaram J of Hepatol 2019

Liver Transplantation in ACLF-3 Model (TAM)

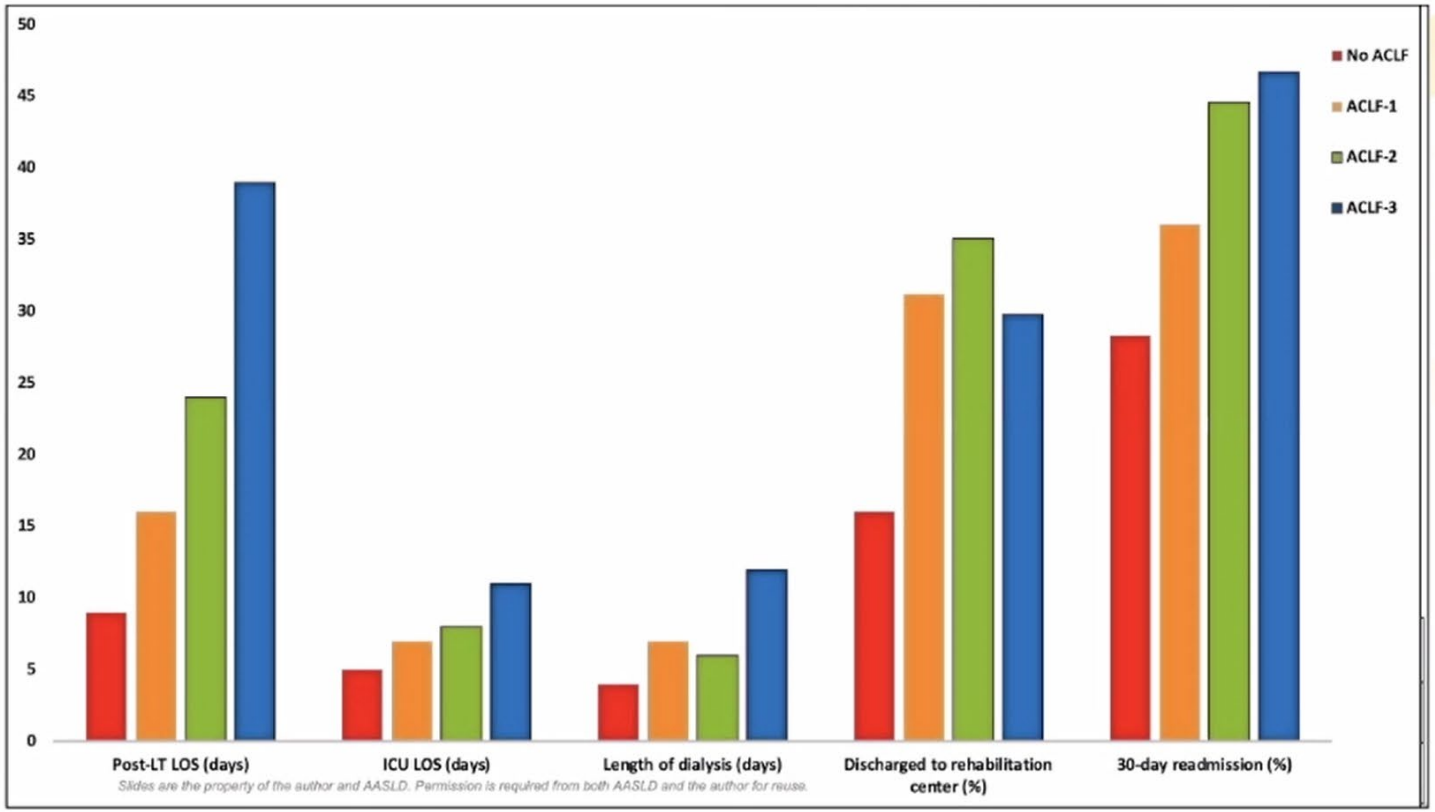
Artzner, T et al. Am J Transplant. 2020 Sep;20(9):2437-2448

Variable	Points
Arterial Lactate < 4 mMol/L Arterial Lactate >/= 4 mMol/L	0 1
Mechanical Vent with PaO2/FiO2 > 200 mm Hg Mechanical Vent with PaO2/FiO2 </= 200 mm Hg	0 1
Age < 53 Age >/= 53	0 1
Leukocyte Count > 10,000 Leukocyte Count </= 10,000	0 1
TOTAL TAM	



EXCELLENT SURVIVAL BUT GREATER POST-TRANSPLANT COMPLICATIONS AND HEALTHCARE RESOURCE UTILIZATION FOR PATIENTS TRANSPLANTED WITH ACUTE-ON-CHRONICLIVER FAILURE

- *Objectives*:
  - To determine post-LT survival among patients with ACLF, compare prevalence of post-LT complications across ACLF grades
- *Methods:*
  - Retrospective data from 10 centers in US 2018-2019 who were in ICU prior to LT
  - ACLF with EASL-CLIF criteria



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Sundaram V, et al. #55

EXCELLENT SURVIVAL BUT GREATER POST-TRANSPLANT COMPLICATIONS AND HEALTHCARE RESOURCE UTILIZATION FOR PATIENTS TRANSPLANTED WITH ACUTE-ON-CHRONICLIVER FAILURE

- *Objectives*:
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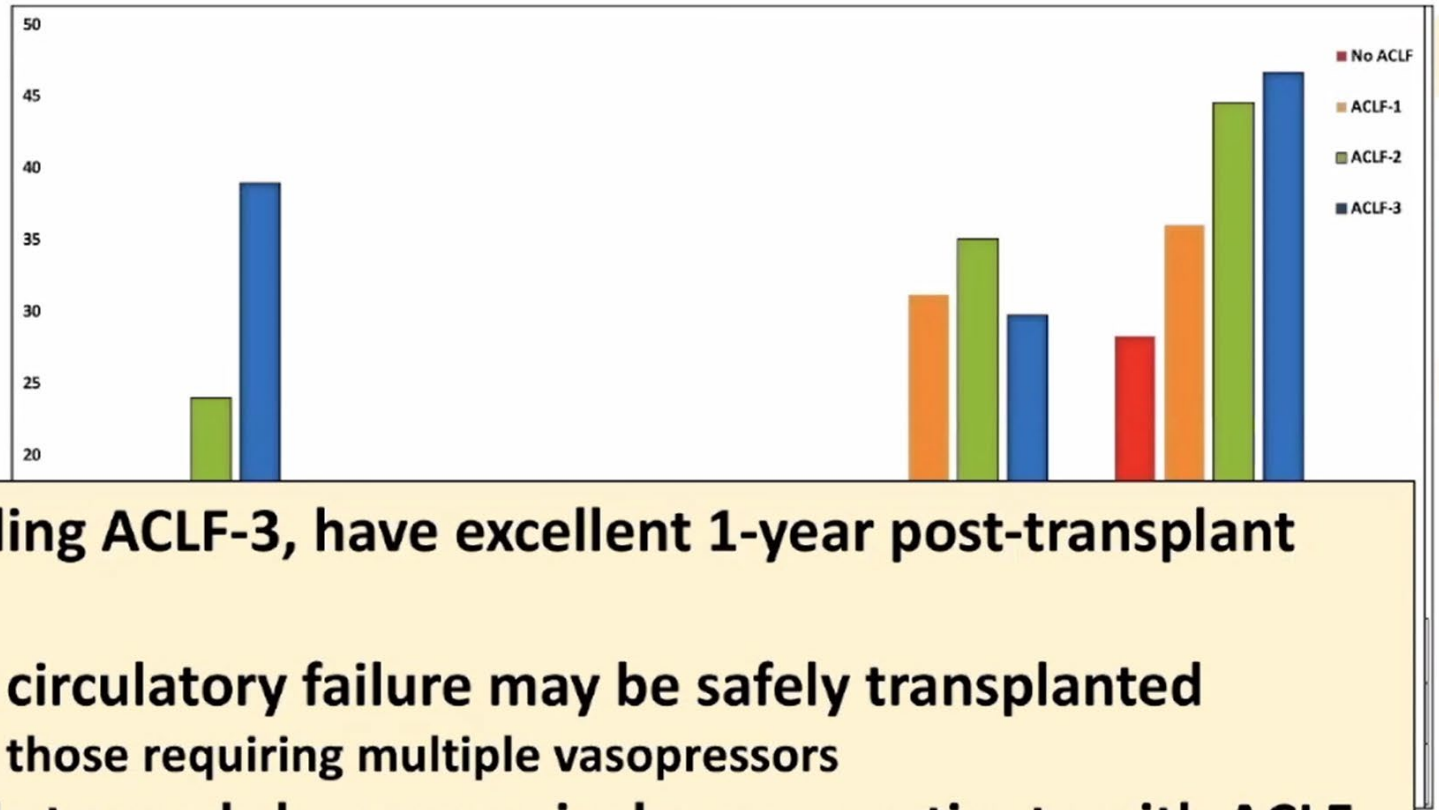
- *Methods*:



- **Patients with ACLF at LT, including ACLF-3, have excellent 1-year post-transplant survival above 85%**
- **Patients with ACLF-3 including circulatory failure may be safely transplanted**
  - **> 80% survival, including among those requiring multiple vasopressors**
- **Although not significant, trends towards lower survival among patients with ACLF-3 and respiratory failure at LT suggests caution in transplanting these patients**
- **Despite good outcomes, significantly greater healthcare utilization significantly greater among patients transplanted with ACLF, across multiple metrics**

CONCLUSION

- The concepts of ACLF are in evolution.
- It is important to recognize ACLF due to its high mortality.
- The most important intervention is to prevent ACLF and to recognize patients at risk of ACLF.
- The treatment of ACLF is not well defined, but they benefit from ICU management and early Liver Transplant evaluation.
- The use of C-CSF is beneficial to a sub-group of these patients.
- Plasma Exchange may be beneficial in a sub-group.

Liver Transplant in ACLF

- CANDIDATES:
  - Patients with ACLF with 1 or 2 organ failures on days 3 to 7, who fail to respond to medical therapy, and
  - Patients with ACLF-3 (limited to 3 to 5 organ failures) who are not in mechanical ventilation, have resolution of at least 1 organ failure and a CLIF-C ACLF Score < 64 at time of organ offer.
- Monitoring:
  - Patients with ACLF-1 and 2 should have daily recalculation of their ACLF Score, and it should be stable or deteriorating, but not reach CLIF-ACLF-3.
  - Patients with ACLF-3 (restricted to 3 to 5 organ failures) should have daily calculated scores and evaluation for any organ failure resolution. If they have at least 1 organ failure resolution, they will be transplantable if their CLIF-C ACLF score is </= 64 and they are not on mechanical ventilation.
  - If on gCSF, the WBC used for calculation should be the one just before gCSF was started. Consider the use of TAM score in the decision.

Liver Transplant in ACLF

- Timing for Evaluation and Listing:
  - Ideally the liver transplant evaluation process will start on day 3 of ACLF.
  - Listing should be as soon as work up completed
- Graft Considerations:
  - Organs with DRI < 1.7 should be used on these patients, and
- Transplantation Timing Considerations:
  - within the initial 30-days after listing if with 1 to 3 organ failures, and
  - within 14 days if they have 4 to 5 organ failures.

Alcohol-Related ACLF
Alcohol Relapse Risk

Approach to Patient with AR-ALF

Maddrey's DF ≥32 + Nonresponse Med Rx
(Lille score >0.45 after 7d)
first liver-decompensating event

- SIPAT Score unk
  HE Stage 3-4
  - Marginal Candidate requiring *extensive* collateral endorsement and commitment
- SIPAT Score <21
  - Good Candidate
- SIPAT Score 21-30
  - Marginal Candidate
- SIPAT Score >30
  - Poor Candidate
    In terms of return to "harmful" drinking

Excellent Post LTx Patient and Graft Survival
Need intensive engagement and support
(Transplant psychiatry, Social Worker, regular PETh after transplant)

Ou

SIPAT psychosocial domains and risk scoring overview.

Psychosocial domains		SIPAT score[a]
Category/domain	Questions	
(A) Patient's readiness level and illness management Score (0–24) ____	1 Knowledge and understanding of medical illness process (that caused specific organ failure)	0–4
	2 Knowledge and understanding of the process of transplantation	0–4
	3 Willingness/desire for treatment (transplant)	0–4
	4 History of treatment adherence/compliance (pertinent to medical issues)	0–8
	5 Lifestyle factors (including diet, exercise, fluid restrictions, and habits according to organ system)	0–4
(B) Social support system level of readiness Score (0–20)____	6 Availability of social support system	0–8
	7 Functionality of social support system	0–8
	8 Appropriateness of physical living space and environment	0–4
(C) Psychological stability and psychopathology Score (0–37) _____	9 Presence of psychopathology (other than personality disorders and organic psychopathology)	0–8
	10 History of organic psychopathology or neurocognitive impairment (i.e., illness or medication-induced psychopathology)	0–5
	11 Influence of personality traits vs. disorder	0–4
	12 Effect of truthfulness vs. deceptive behavior	0–8
	13 Overall risk for psychopathology	0–4
(D) Lifestyle and effect of substance use Score (0–29) _____	14 Alcohol use, abuse, and dependence	0–8
	15 Alcohol abuse - risk for recidivism	0–4
	16 Illicit substance, abuse and dependence	0–8
	17 Illicit substance abuse - risk for recidivism	0–4
	18 Nicotine use, abuse, and dependence	0–5

a Lower scores indicate lower risk e.g. 0 = excellent/low risk, 4 = poor/high risk.

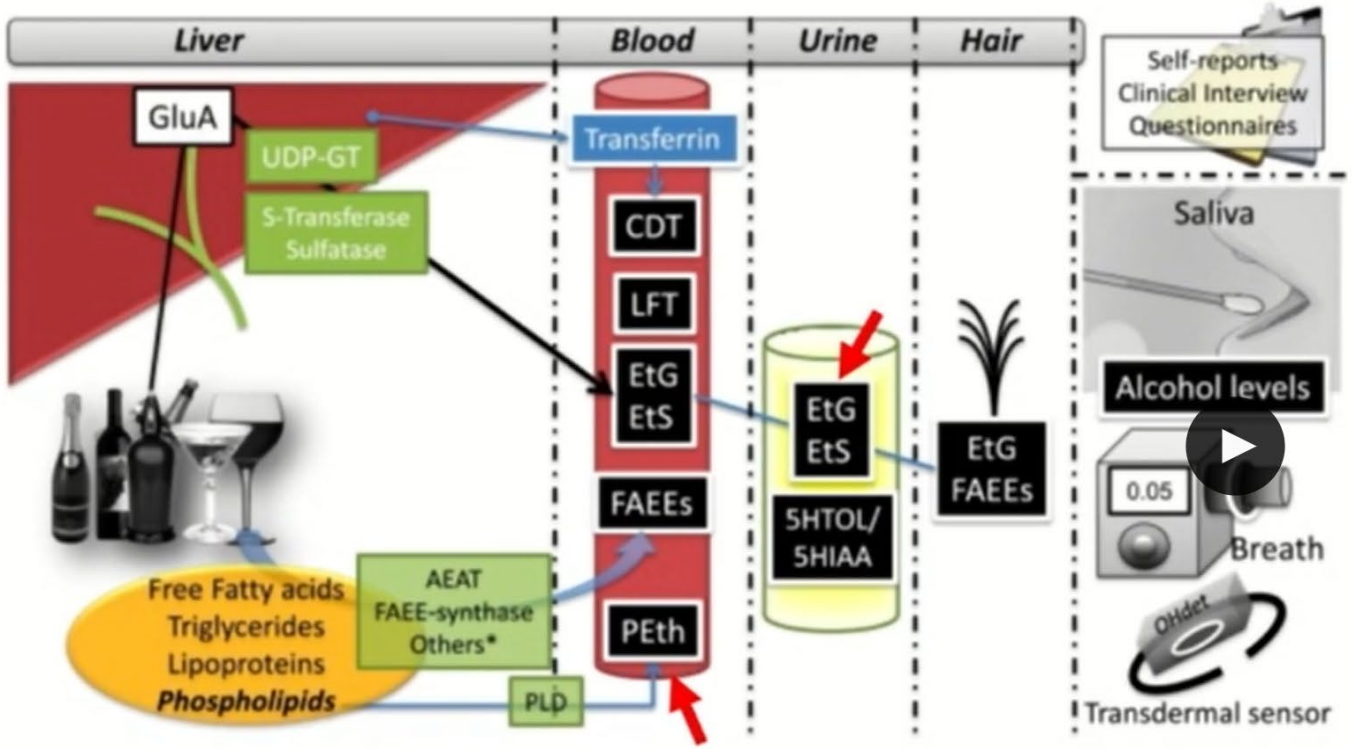
SIPAT SCORING

Risk scoring Total risk score	Candidate rating	Recommendation
0–6	Excellent	List without reservation
7–20	Good	List, although monitoring of identified risk factors may be required
21–39	Minimally acceptable candidate	List under certain conditions: Identified risk factors must be satisfactorily addressed before representing
40–68	High risk Significant risks identified	Defer listing while identified risks are satisfactorily addressed
>69	Poor	Listing not recommended while identified risk factors present

[a] Lower scores indicate lower risk e.g. 0 = excellent/low risk, 4 = poor/high risk.

Biomarkers of alcohol use

GGT +
AST>ALT



EtG >100 ng/mL
EtS >25 ng/mL

PEth

- Light or NO (<20 ng/mL)
- Significant (20–199 ng/mL)
- Heavy (>200 ng/mL).

Cabezas, Lucey & Bataller, Clin Liver Dis 2017

AASLD The Liver Meeting®

Invasive Procedures in ACLF

SIR Peri-procedural Thrombotic and Bleeding Risk Management Guidelines

Patel, IJ et al. J Vasc Interv Radiol 2019; 30:1168–1184

ALL PATIENTS – High Bleeding Risk Procedures

- **Screening Coagulation Laboratory Test High bleeding risk**
  - PT/INR:
    - routinely recommended
  - Fibrinogen:
    - Routinely recommended
  - Platelet count/hemoglobin:
    - routinely recommended
- Thresholds
  - INR: correct to within range of < 2.5
  - Platelets: transfuse if < 50,000
  - Fibrinogen > 100 mg/dL

- Ablations: solid organs, bone, soft tissue, lung
- Arterial interventions: > 7-F sheath, aortic, pelvic, mesenteric, CNS†,‡
- Biliary interventions (including cholecystostomy tube placement)
- Catheter directed thrombolysis (DVT, PE, portal vein)**
- Deep abscess drainage (eg, lung parenchyma, abdominal, pelvic, retroperitoneal)
- Deep non-organ biopsies (eg, spine, soft tissue in intraabdominal, retroperitoneal, pelvic compartments)
- Gastrostomy/gastro-jejunostomy placement
- IVC filter removal complex**
- Portal vein interventions
- Solid organ biopsies
- Spine procedures with risk of spinal or epidural hematoma (eg, kyphoplasty, vertebroplasty, epidural injections, facet blocks cervical spine)§
- Transjugular intrahepatic portosystemic shunt††
- Urinary tract interventions (including nephrostomy tube placement, ureteral dilation, stone removal)
- Venous interventions: intrathoracic and CNS interventions

Cryoprecipitate for Fibrinogen < 120 mg/dL and Platelets if < 50,000
FFP is not useful in correcting PT/INR in cirrhosis

ALL PATIENTS – Low Bleeding Risk Procedures

- **Screening Coagulation Laboratory Test Low bleeding risk**
  - PT/INR:
    - not routinely recommended
  - Platelet count/hemoglobin:
    - not routinely recommended
  - Fibrinogen:
    - recommended
- Thresholds
  - INR: not indicated
  - Platelets: transfuse if < 20,000
  - Fibrinogen > 100 mg/dL

- Catheter exchanges (gastrostomy, biliary, nephrostomy, abscess, including gastrostomy/ gastro-jejunostomy conversions)
- Diagnostic arteriography and arterial interventions: peripheral, sheath < 6 Fr, embolo-therapy‡
- Diagnostic venography and select venous interventions: pelvis and extremities
- Dialysis access interventions
- Facet joint injections and medial branch nerve blocks (thoracic and lumbar spine)§
- IVC filter placement and removal k
- Lumbar puncture¶
- Non-tunneled chest tube placement for pleural effusion
- Non-tunneled venous access and removal (including PICC placement)
- Paracentesis
- Peripheral nerve blocks, joint, and musculoskeletal injections§
- Sacroiliac joint injection and sacral lateral branch blocks§
- Superficial abscess drainage or biopsy (palpable lesion, lymph node, soft tissue, breast, thyroid, superficial bone, eg, extremities and bone marrow aspiration)
- Thoracentesis
- Transjugular liver biopsy (plat > 30,000)

Cryoprecipitate for Fibrinogen < 120 mg/dL and Platelets if < 20,000

Suggested Laboratory Thresholds for Performance of a Procedure in Patients with Chronic Liver Disease

Procedure Risk	INR	Platelets *	Fibrinogen (mg/dL) **
Low	N/A	> 20,000	> 100
High	< 2.5	> 30,000	> 100

* One unit of apheresis or 4-6 pooled from whole blood donors) increases the platelet count by 25–50 x 10^9/L in normal-sized patient without splenomegaly

** Administer 1 dose cryoprecipitate (bodyweight < 80 kg) or 2 doses (body weight > 80 kg)