Acute on Chronic Liver failure

Bilal Bobat
Liver unit WDGMC

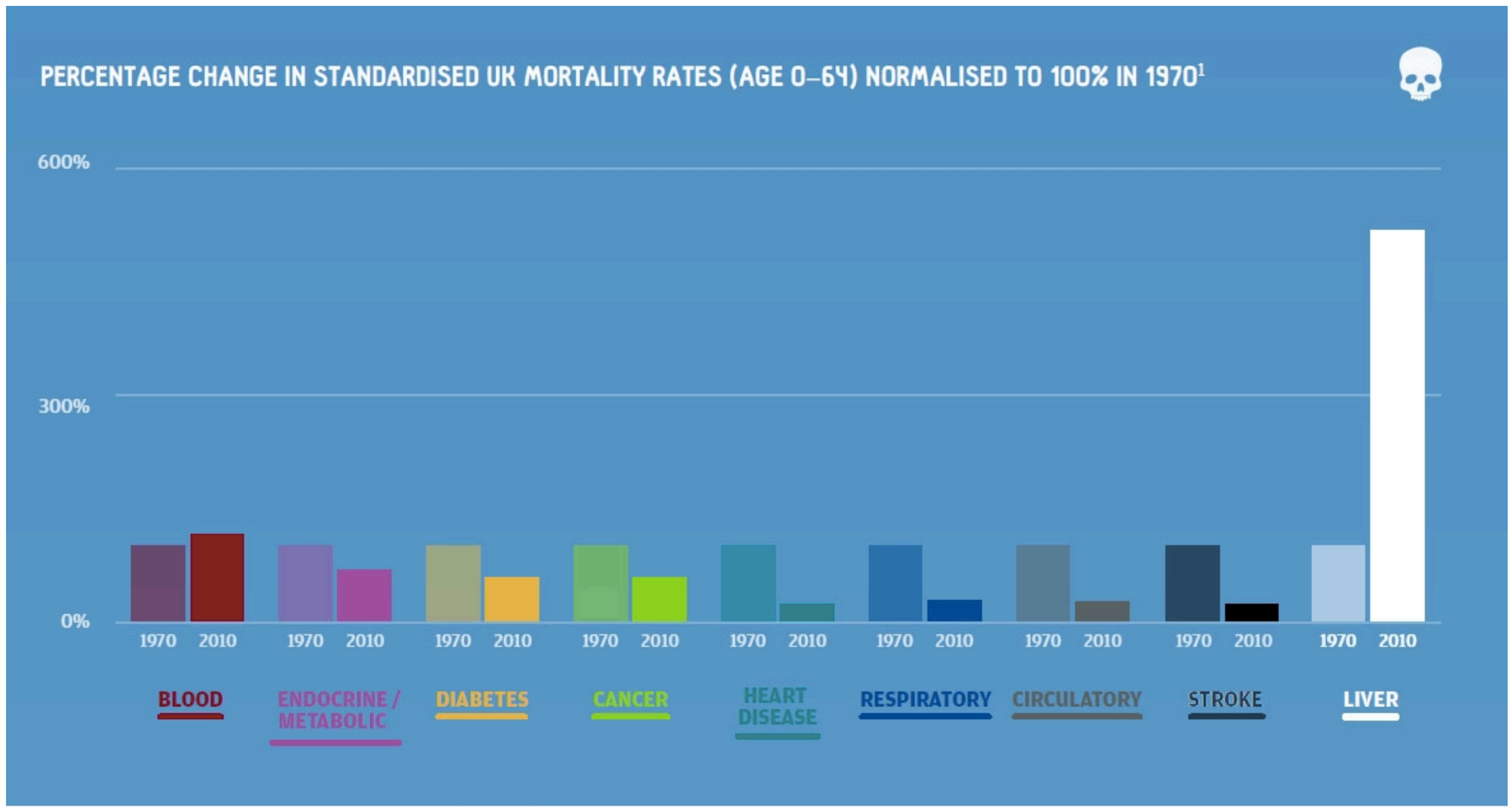
Wits University Donald Gordon Medical Centre
Patient-centred. Independent. Academic.

MEDICLINIC

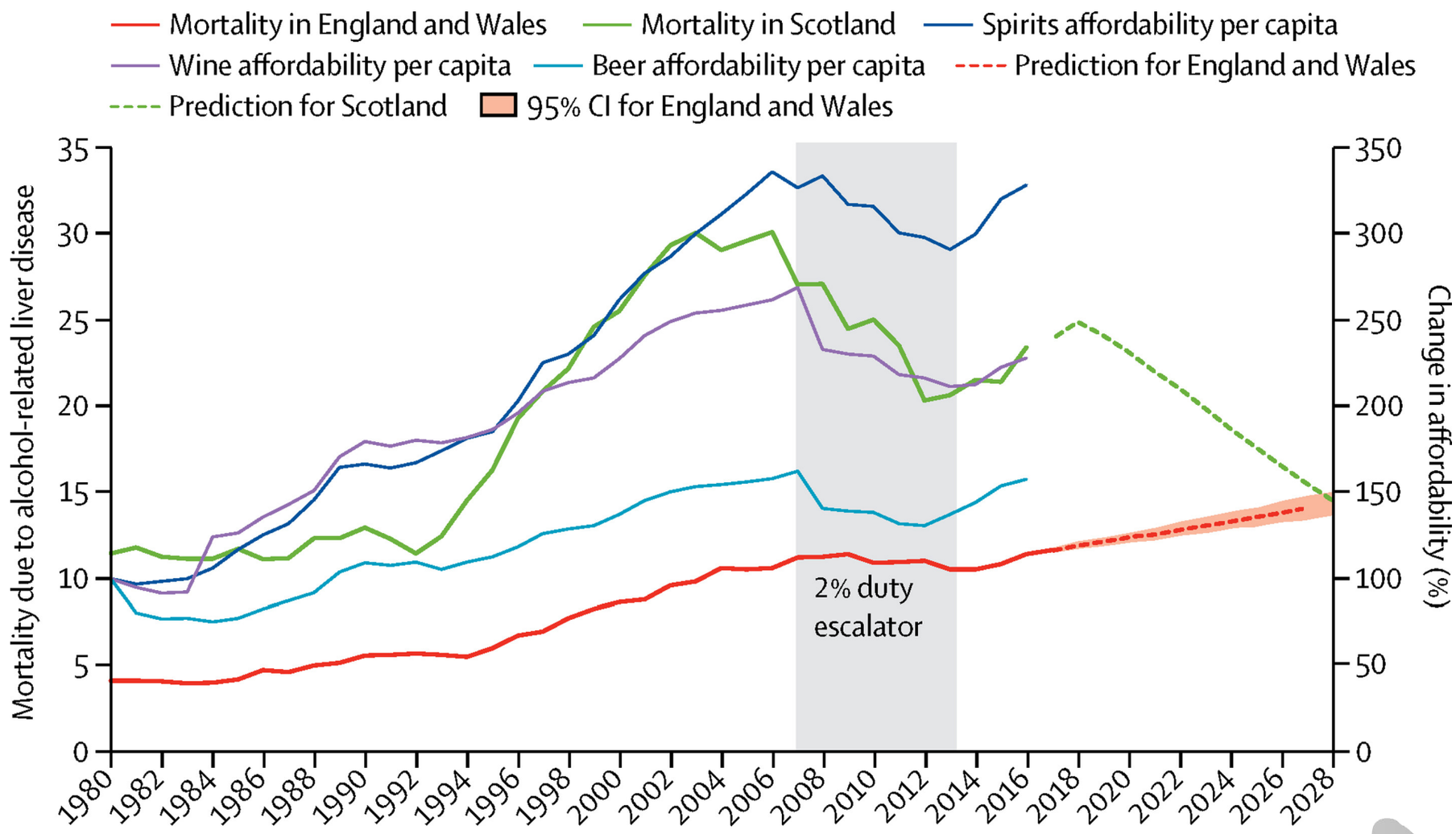
WITS TRANSPLANT
Progressive medicine, exceptional care.

Just how big a problem is it?

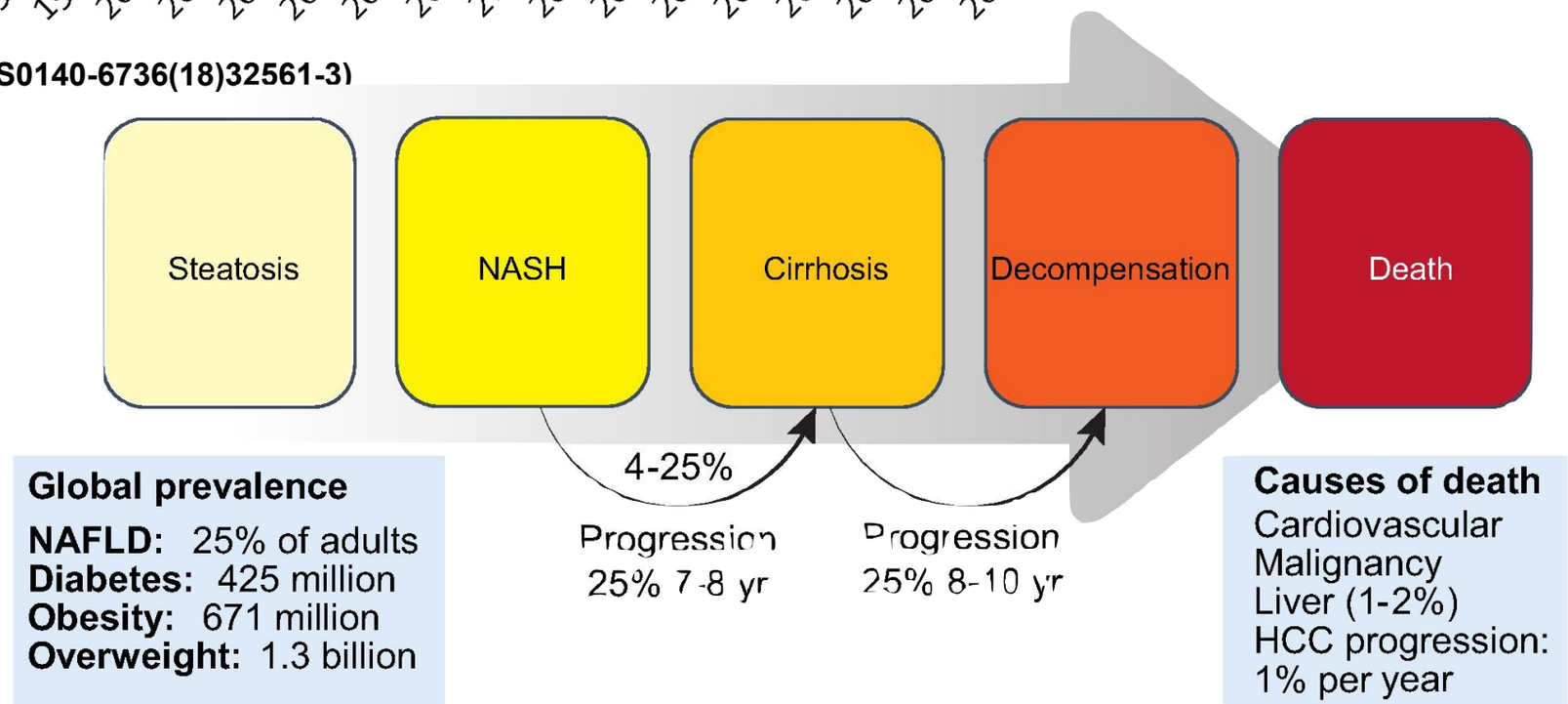
- Cirrhosis rising global problem: 10.4% (CI: 9·0 to 11·6) [1]
- South Africa: Cirrhotic deaths up by 34% 1990-2010 [2]



1. GBD 2016 Causes of Death Collaborators, *Lancet* (2017) 390, P1151-1210,
2. Wong, M.C.S. & Huang, *J. Hepatol Int* (2018) 12: 201.



The Lancet 2018 392, 2398-2412DOI: (10.1016/S0140-6736(18)32561-3)



J. Hepatology **Vol 70, Issue 1, January 2019, 151-171**

Patient Profile

- 15% Progress to Decompensation each year
- Variceal bleed alone - 20%
- Non Variceal risk of Decompensation - 24%
- 2 Decompensating events - 50-78%
- Cost: UK: ICU £50 000 per survivor
  US: Care of In Patient Cirrhotics - $3bn yearly

Definitions

- Acute Decompensation: Occurrence of one of or a combination of Hepatic Encephalopathy, Ascites or Gastrointestinal bleeding

- Acute Liver Failure: Presence of Hepatic Encephalopathy and Coagulopathy with an INR of >1.5

Definitions - ACLF

- WHO: ACLF is a syndrome characterised by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the INR) and one or more extrahepatic organ failures that is associated with increased mortality within a period of 28 days and up to 3 months from onset

- APASL: Liver failure is defined as jaundice (a serum bilirubin level of ≥5 mg/dL) and coagulopathy (an INR of ≥1.5 or prothrombin activity of <40%). Liver failure is complicated within 4 weeks by clinical ascites and/or encephalopathy in patients with previously diagnosed or undiagnosed chronic liver disease (including cirrhosis)

Definitions

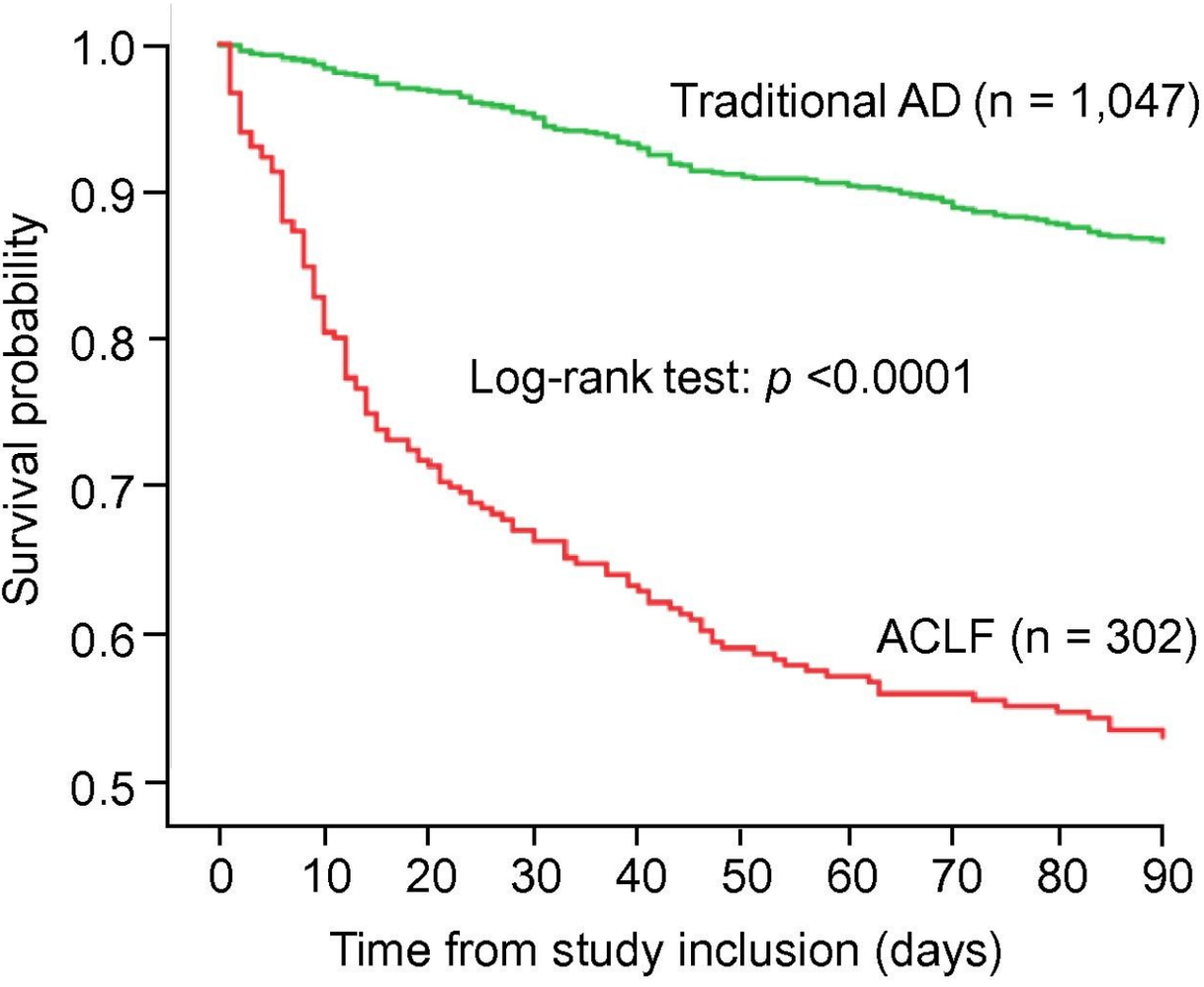
- EASL-CLIF: A syndrome of Acute decompensation with the presence of Organ Failure as defined by a Modified SOFA score accompanied by a high mortality.

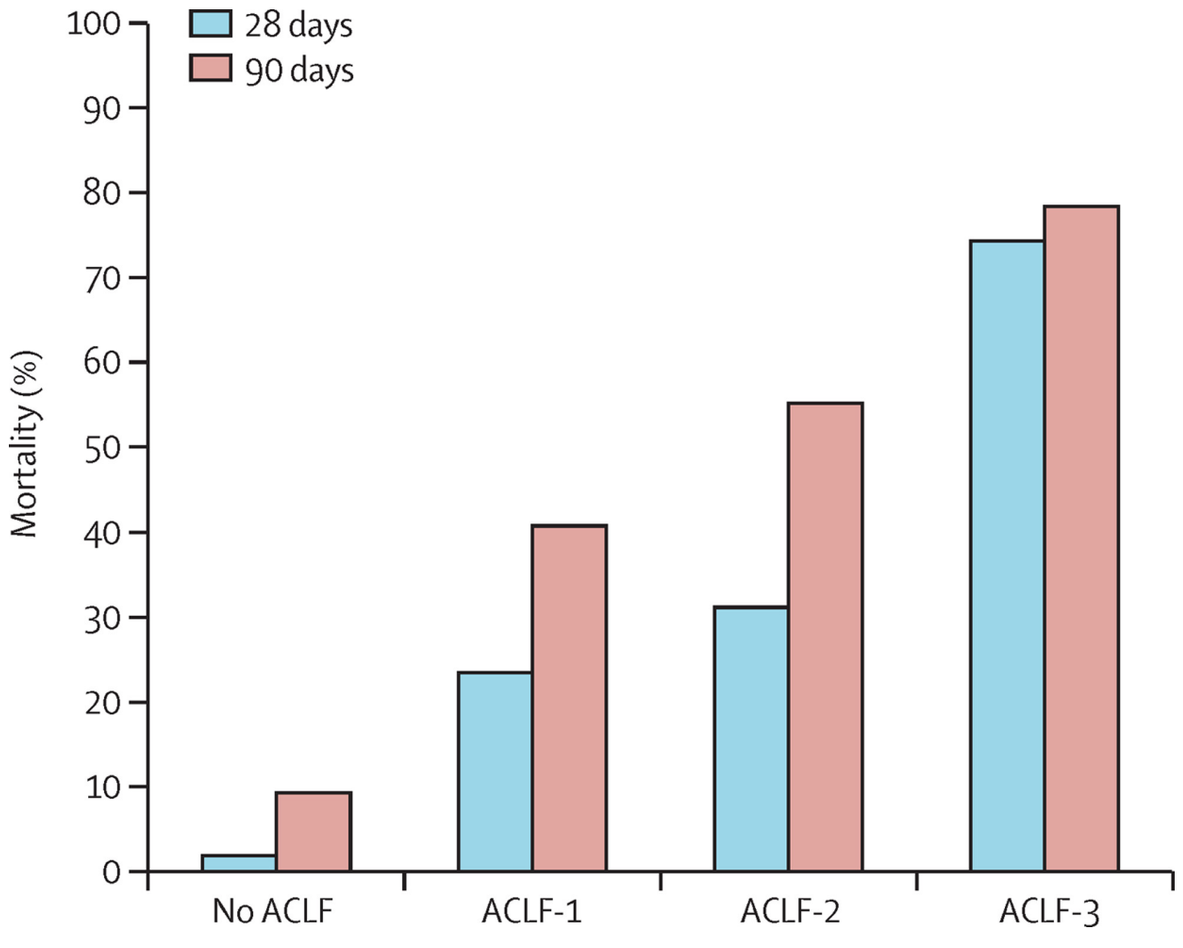
CLIF Organ Failure Score

		Score = 1	Score = 2	Score = 3
Liver (Bilirubin)		<103µmol/L	104-206µmol/L	>206µmol/L
Kidney (Creatinine)		<175µmol/L	176-310µmol/L	>310µmol/L
Brain (West-Haven HE Grade)		0	1-2	3-4
Circulation (MAP)		>70mmHg	<70mmHg	Vasopressors
Respiratory	PaO_2 / FiO_2	>300	201-300	<200
	SpO_2 / FiO_2	>357	215-357	<214

A score of 3 is the definition of organ failure for all systems except renal for which a score of 2 meets the definition

CLIF Organ Failure Score

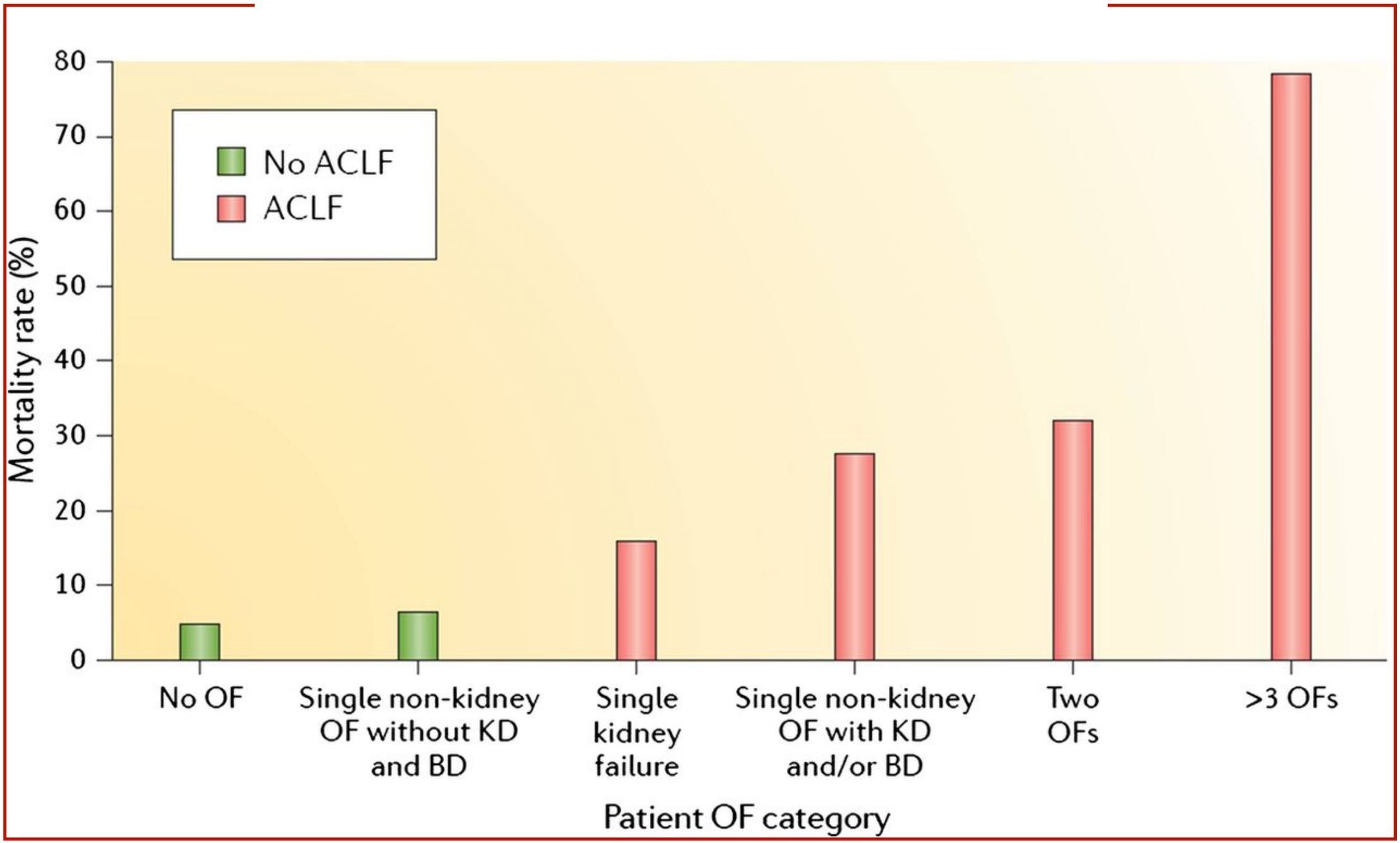




Journal of Hepatology **2018 69, 1384-1393**

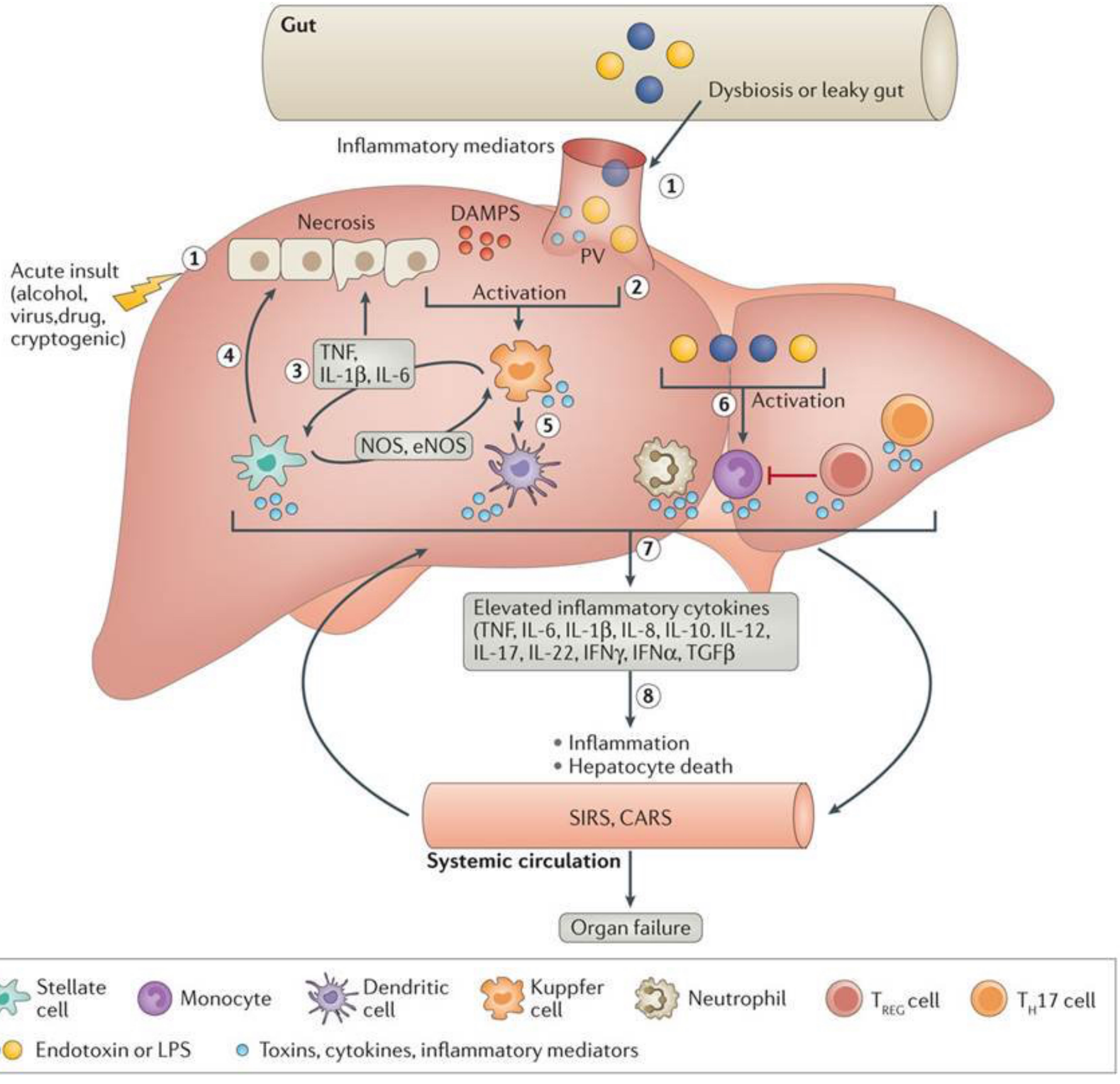
Gastroenterology **2013 Vol: 144, 7, 1426-1437.e9**

Relationship between organ failure and mortality in acute-on-chronic liver failure (ACLF).

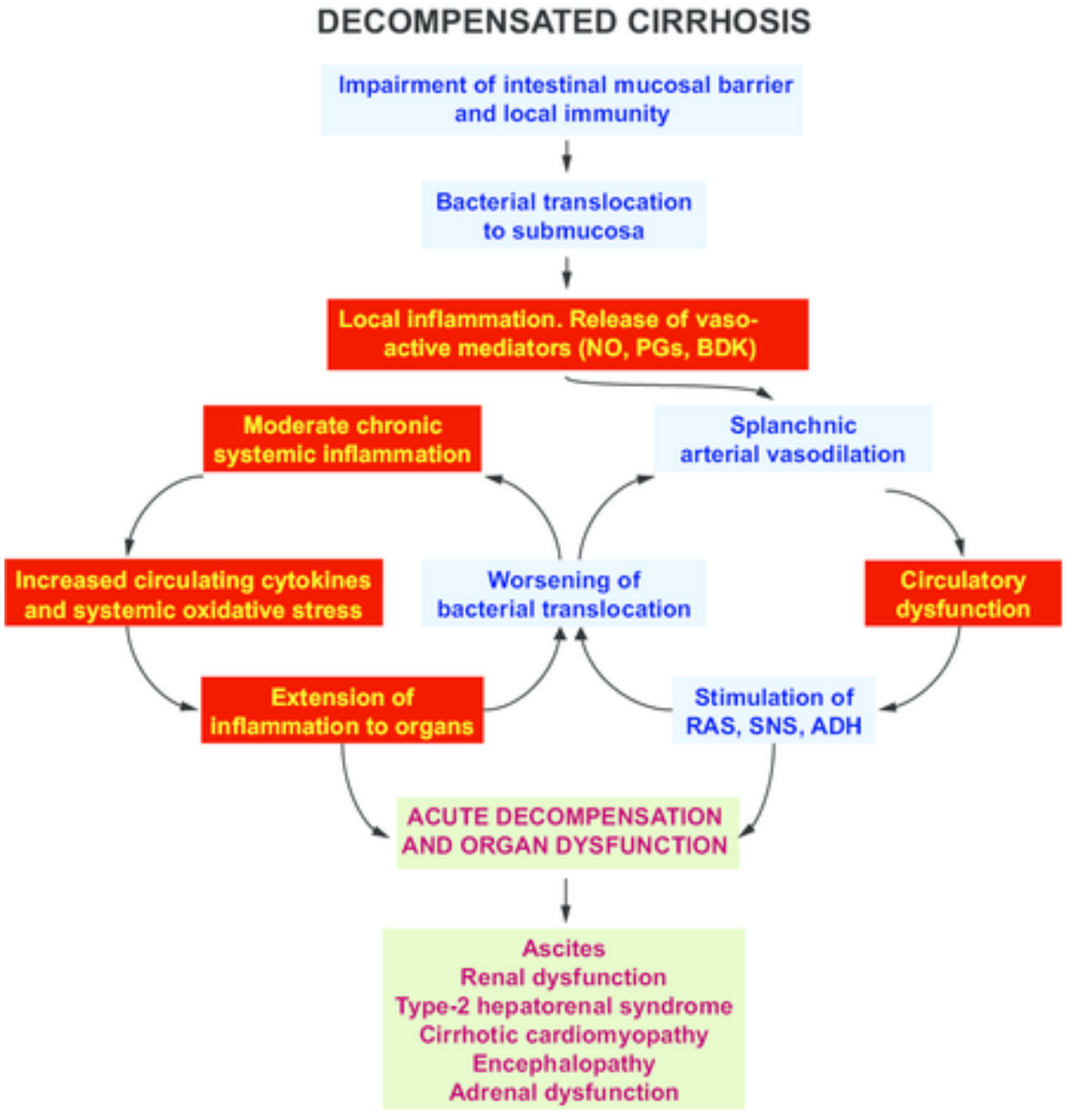


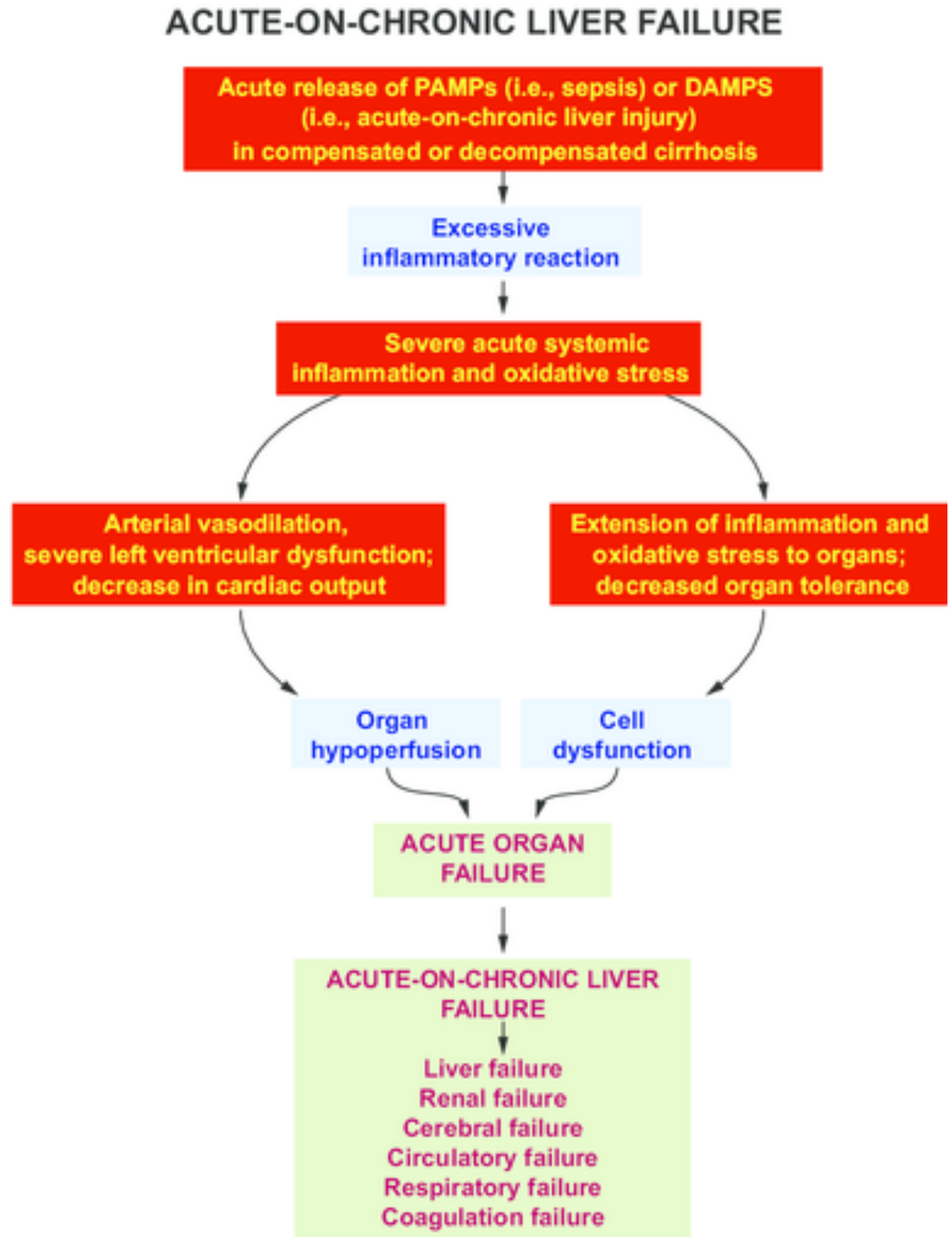
Ruben Hernaez et al. Gut 2017;66:541-553

GUT


Gut
Dysbiosis or leaky gut
Inflammatory mediators
1
Necrosis
DAMPS
PV
Acute insult
(alcohol,
virus,drug,
cryptogenic)
1
Activation
2
4
3
TNF,
IL-1β, IL-6
6
Activation
5
NOS, eNOS
7
Elevated inflammatory cytokines
(TNF, IL-6, IL-1β, IL-8, IL-10. IL-12,
IL-17, IL-22, IFNγ, IFNα, TGFβ
8
• Inflammation
• Hepatocyte death
SIRS, CARS
Systemic circulation
Organ failure
Stellate cell
Monocyte
Dendritic cell
Kuppfer cell
Neutrophil
T REG cell
T H 17 cell
Endotoxin or LPS
Toxins, cytokines, inflammatory mediators

Pathogenesis

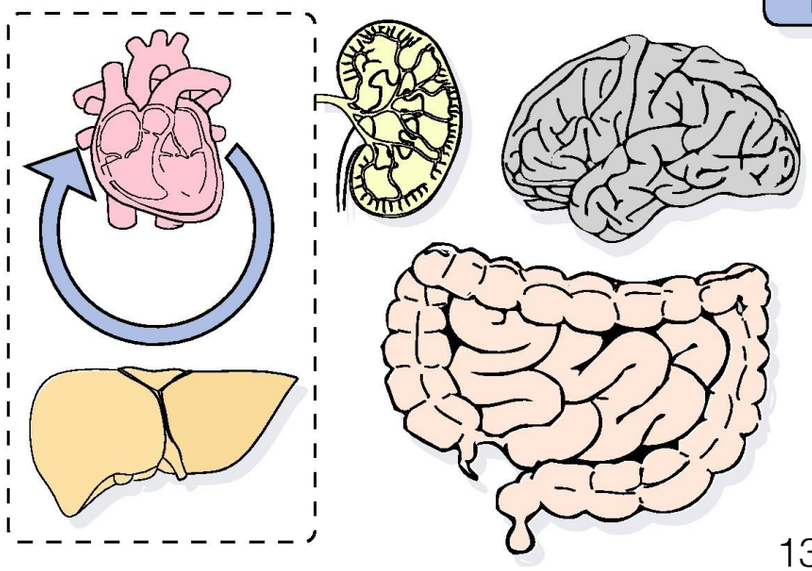




Journal of Hepatology Volume 63, Issue 5, November 2015, 1272-1284

Pathogenesis

The **PIRO** concept of acute-on chronic liver failure		Assessment	Intervention
Predisposition	Severity of cirrhosis	• Aetiology • Pugh score • MELD • [Biomarkers]	Early identification Risk stratification Preventative strategies [Novel interventions]
Injury	Precipitating event	• Hepatic • Extra-hepatic • [Therapies]	Rapid intervention to treat event Bundles of care [Novel interventions]
Response	Inflammation	• Inflammation • Immune failure • [Biomarkers]	Vigilance, monitoring Goal directed approaches [Biomarkers and novel interventions]
Organ	Organ failure	• SOFA • APACHE • [Biomarkers]	Intensive care, organ support Liver transplantation [Liver support, stem cell therapies]



Journal of Hepatology 2012 vol. 57 j 1336–1348

Precipitants

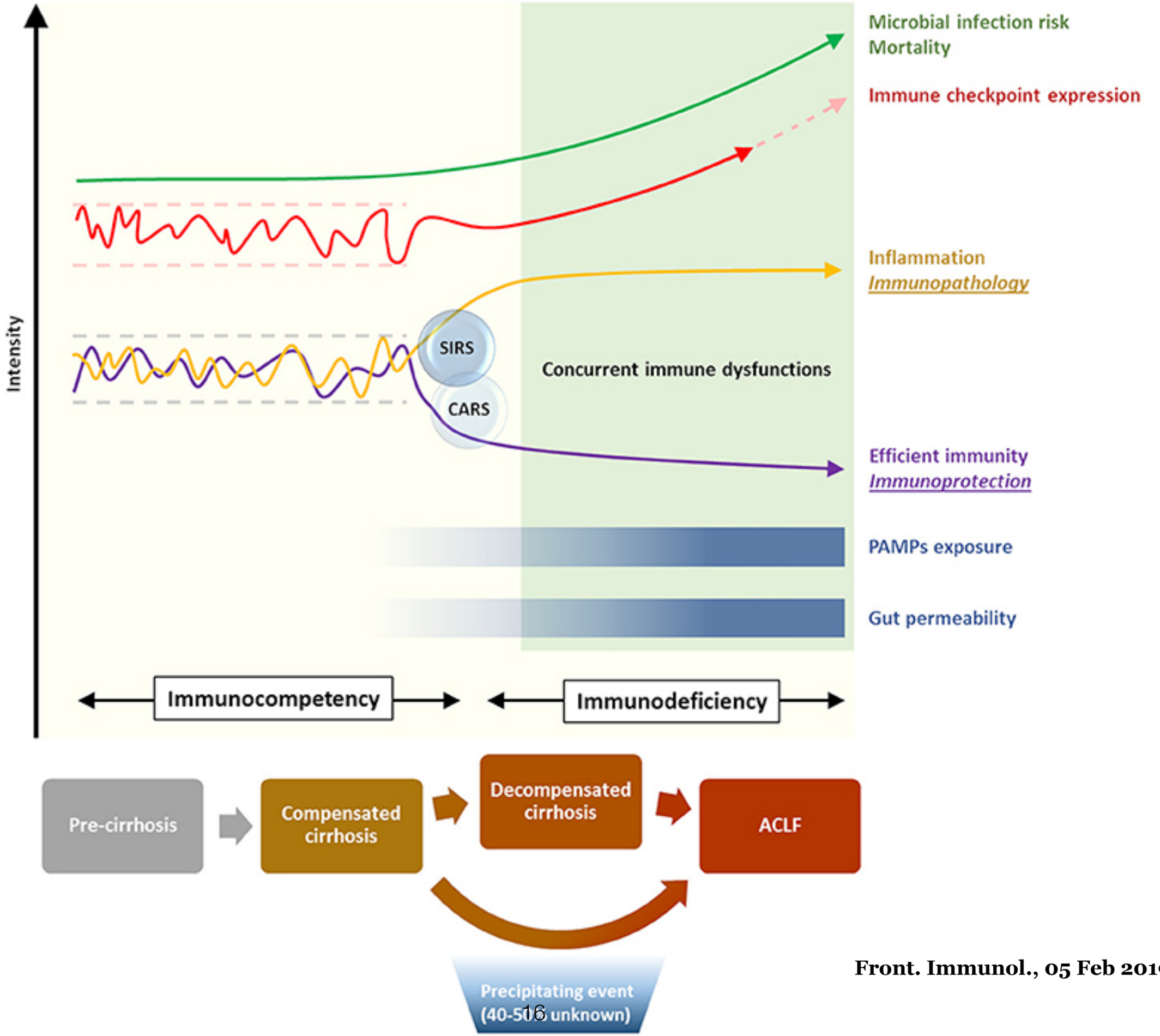
Event	Traditional AD N=1040	ACLF N=343	All Patients (N=1343)
Bacterial Infection	226 (21.8)	98(32.6)	324 (24.1)
Active Alcoholism	147 (14.9)	69(24.5)	216(16.1)
Gastrointestinal Haemorrhoage	180(17.3)	40(13.2)	220(16.4)
Other Event	34(3.5)	25(8.6)	59(4.4)
More than 1 Event	56(5.7)	39(13.5)	95(7.1)
No Event	584(58.9)	126(43.6)	710(52.9)

Precipitating events in patients with traditional AD, ACLF and in the whole cohort Canonic study

Gastroenterology 2013 Vol: 144, 7, 1426-1437.e9

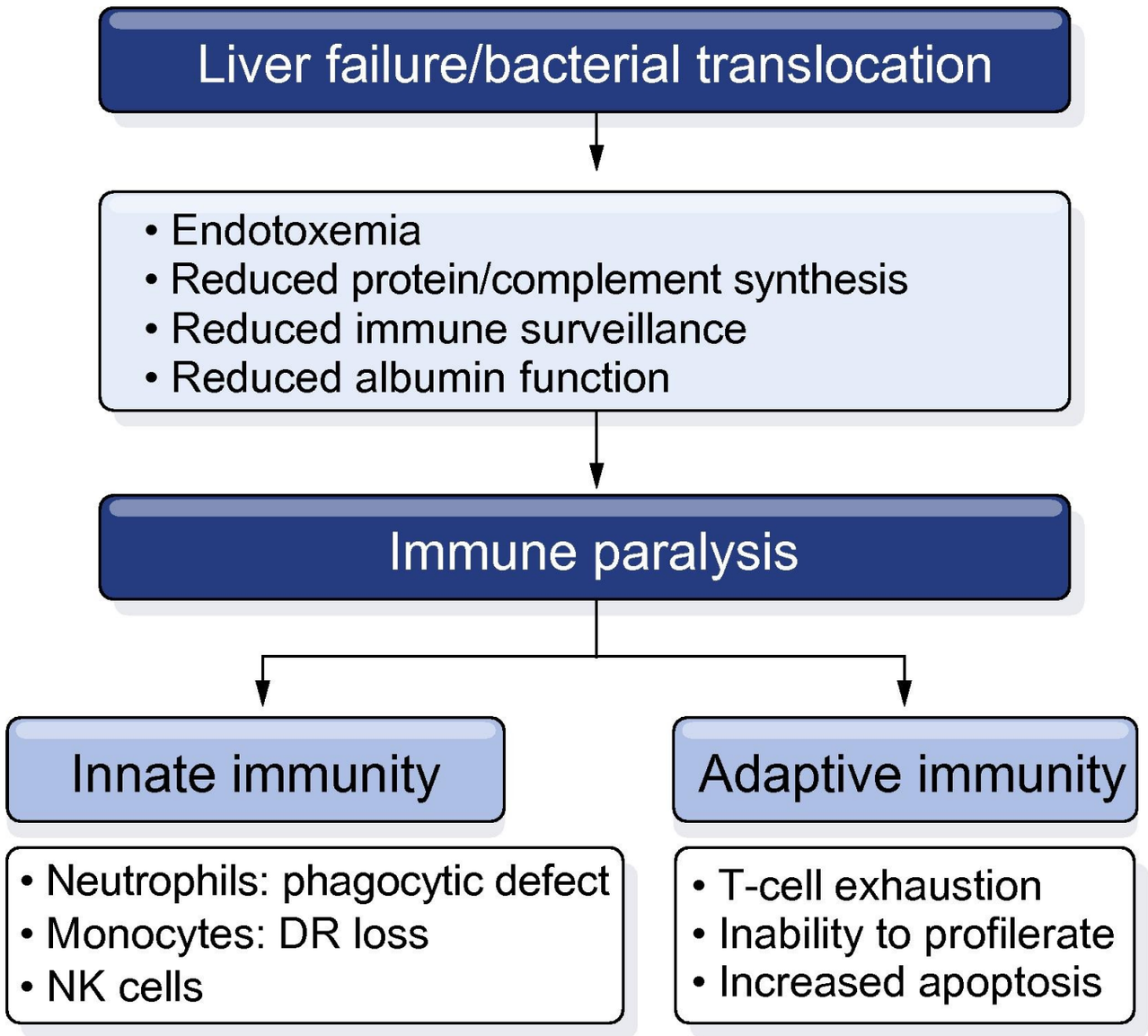
Precipitants - Infection

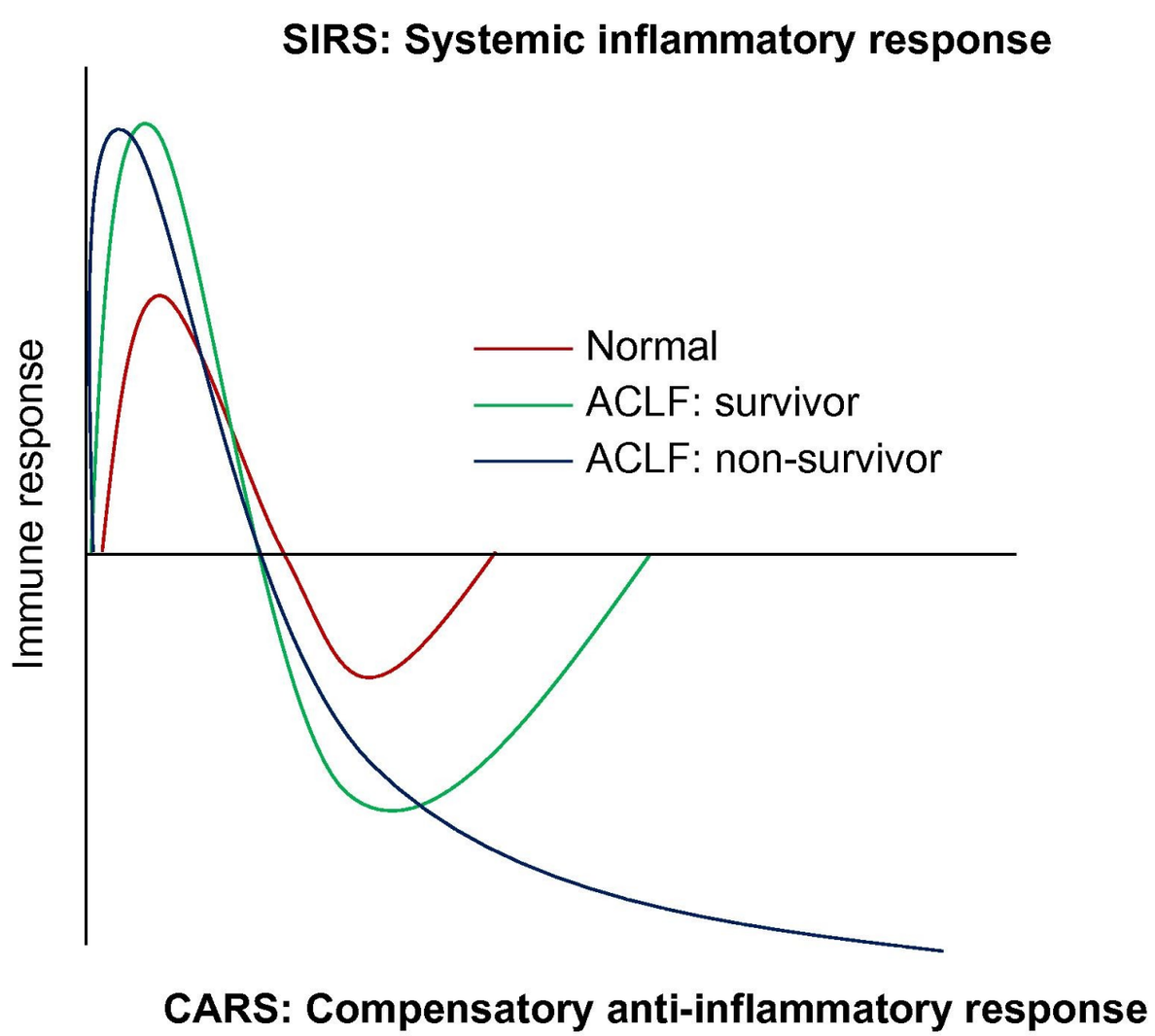
- 40-50% of hospital admissions for cirrhosis
- Mortality 15% - Double those without
- Variable according to geographical location



Front. Immunol., 05 Feb 2019

Immune Paresis





Journal of Hepatology 2012 vol. 57 j 1336–1348

Organ Failures: Liver

- Hyperbilirubinaemia and Coagulopathy
- Bile stasis linked to increased infection
- Liver Inflammation α Portal pressure

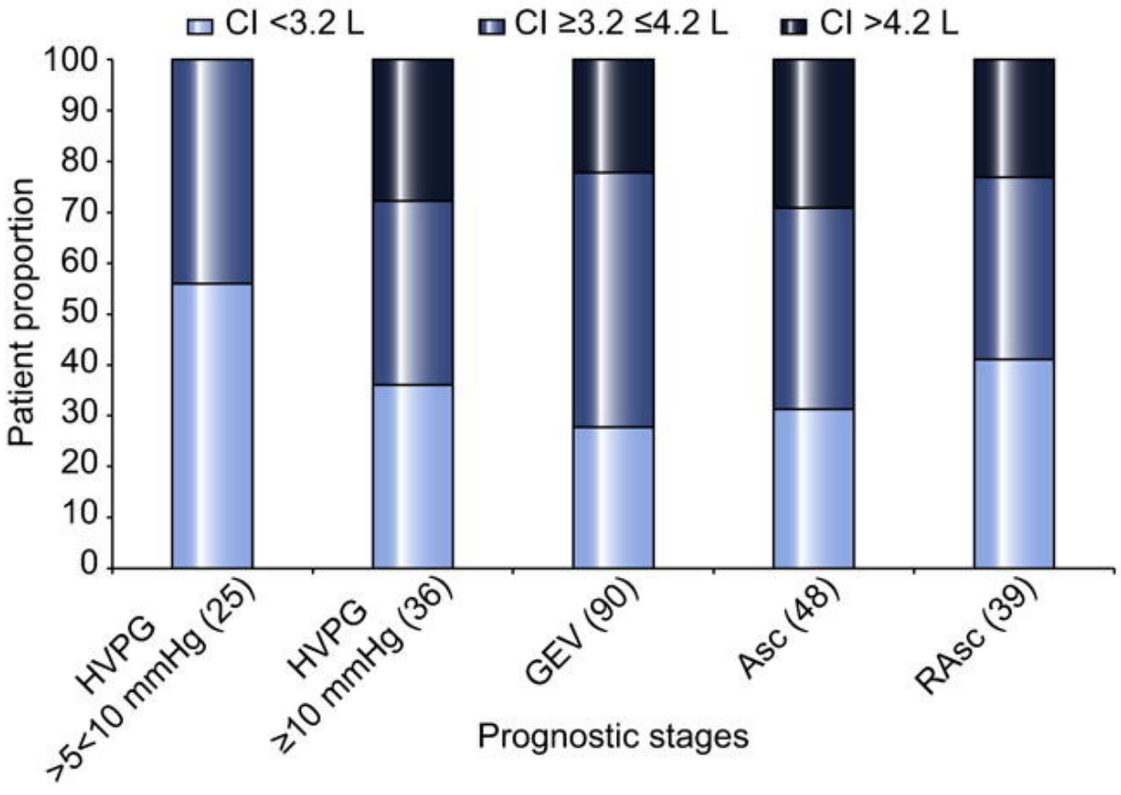
OF - Heart

- Cirrhosis associated with an increased cardiac output
- Increased Blood volume but abnormally distributed
- Poor response to Fluid challenge
    - Albumin choice of fluid
- Blunted Effect to Inotropes
    - Noradrenaline inotrope of choice
- Require Invasive monitoring to guide resuscitation
- Circulatory failure linked to High Mortality rate

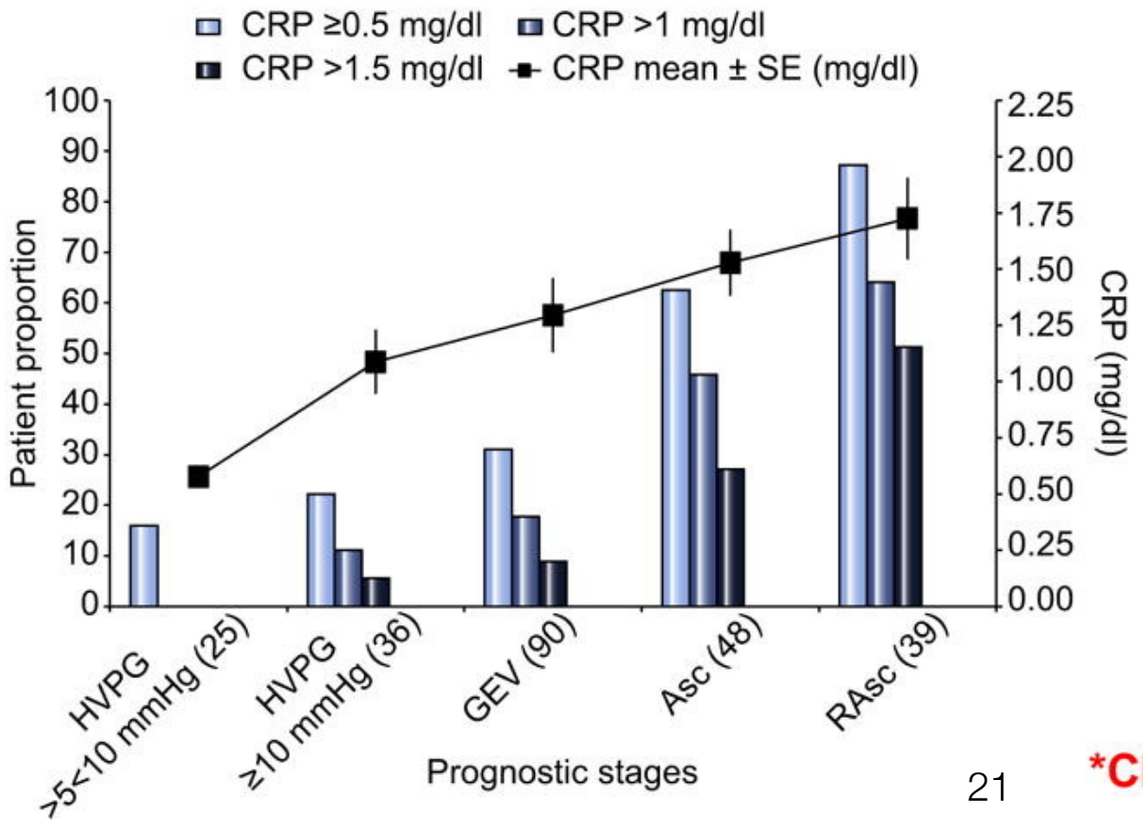
OF - Cirrhotic Cardiomyopathy

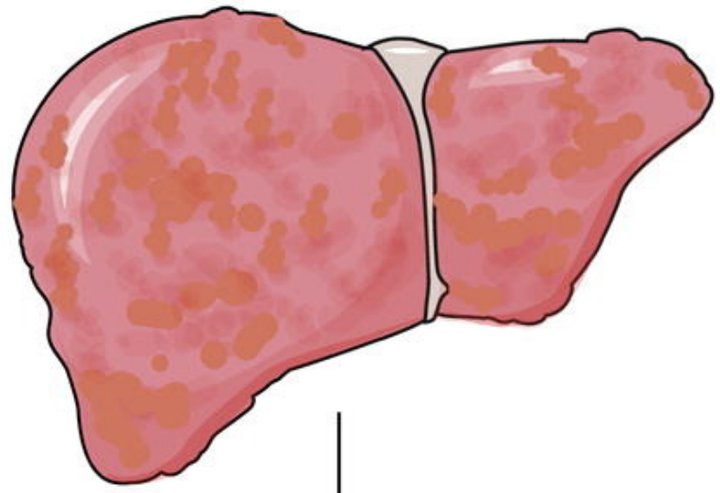
- CCM occurs in patients with established cirrhosis characterized by:
  - Blunted contractile response to stress (pharmacological/ surgery or inflammatory)
  - Altered diastolic left ventricular relaxation or/and increased left atrial volume
  - Electrophysiological abnormalities e.g. prolonged QTc
  - Cardiac output tending to decrease with decompensation
  - Systolic dysfunction: LVEF <55%

Cardiodynamic states in the five prognostic stages of cirrhosis (CI, cardiac index)



Circulating C reactive protein (CRP) in the five prognostic stages of cirrhosis





CSPH*

High CRP **Low/High CI**

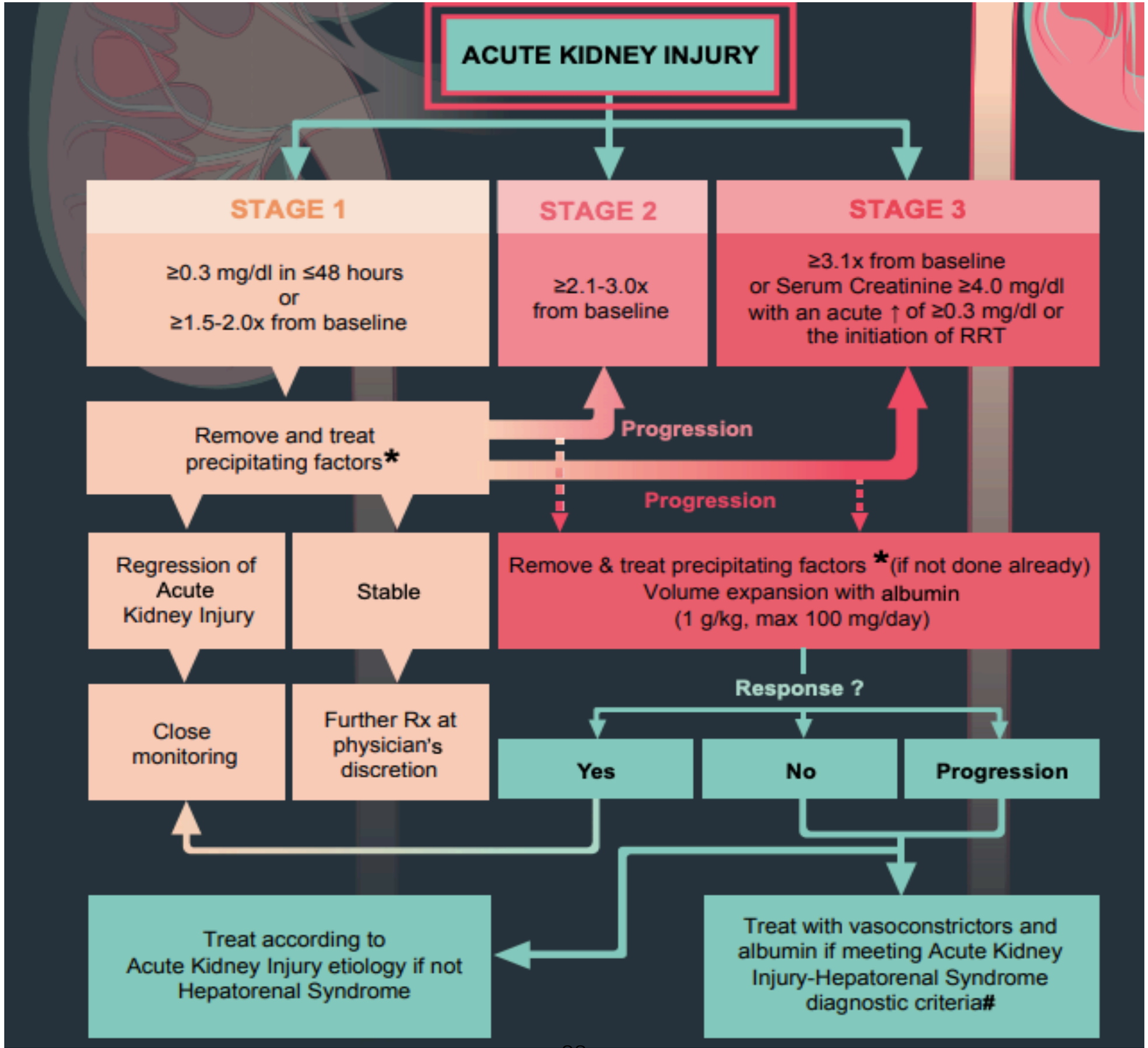
Increased risk of decompensation and death

Hepatology,Vol68, 5, May 2018, 949-958

*Clinically significant portal hypertension

OF - Renal

- HepatoRenal Syndrome
    - Type I: 2 fold increase in baseline creatinine or a level greater than 221µmol/l
    - Type II: Slow Increase to a creatinine of >133µmol/l with uNa <10µmol/l
    - AKI-HRS

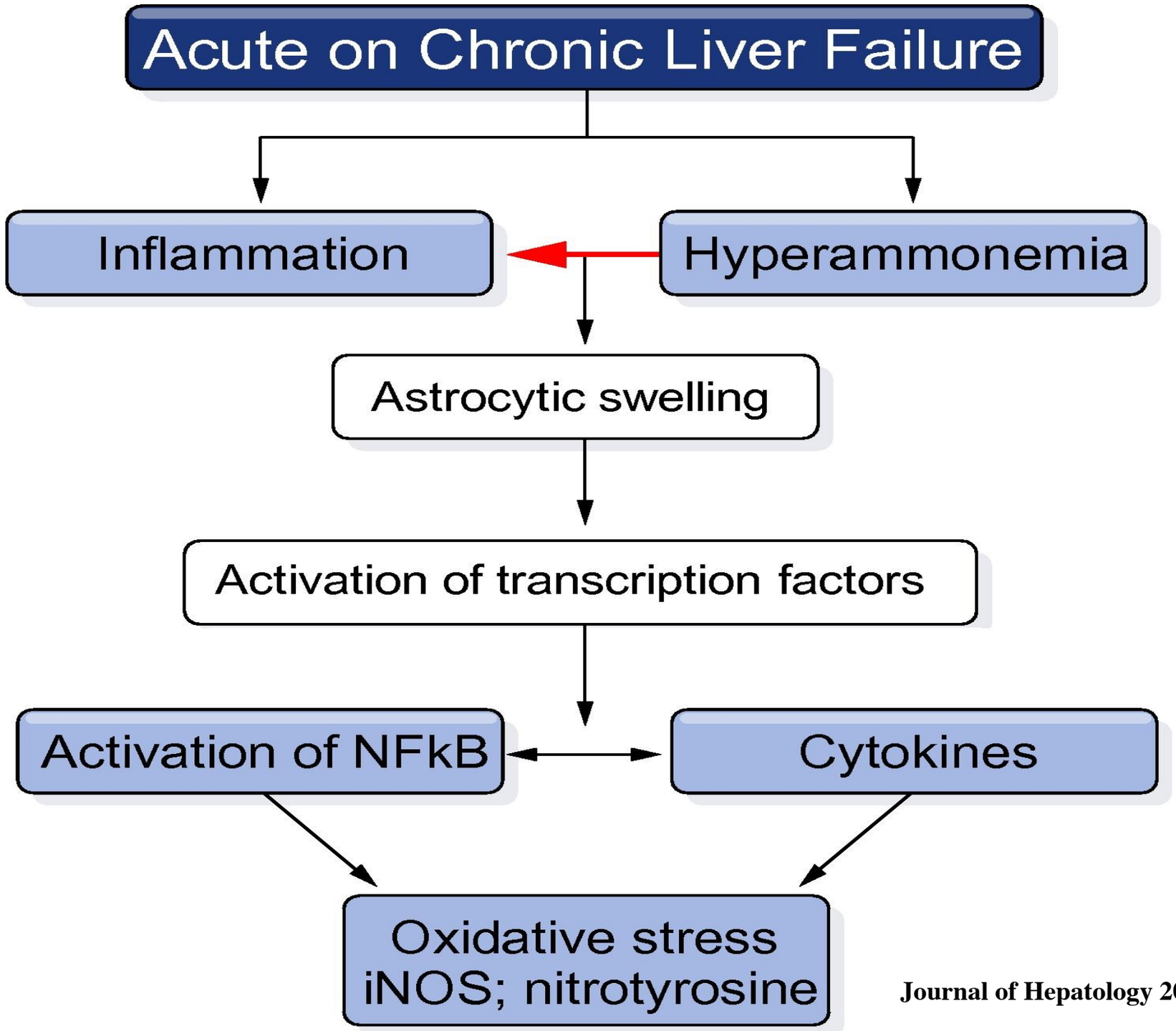


Kidney International (2017)92, 1058–1070;

AKI-HRS

- IV Albumin and vasopressors
- Advanced ACLF-3 - Blunted response to inotropes
- CRT preferred over intermittent HD

OF - Cerebral



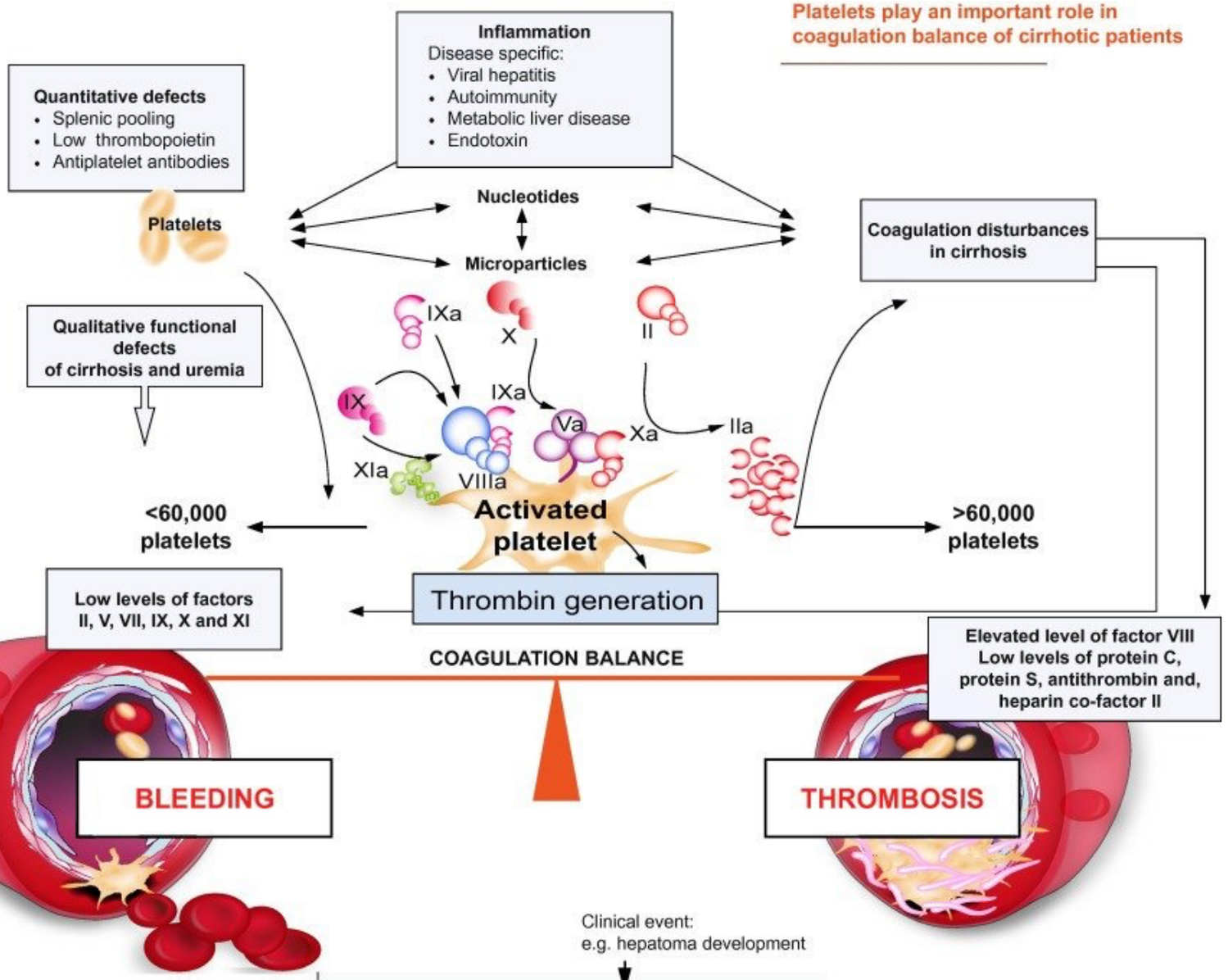
Journal of Hepatology 2012 vol. 57 j 1336–1348

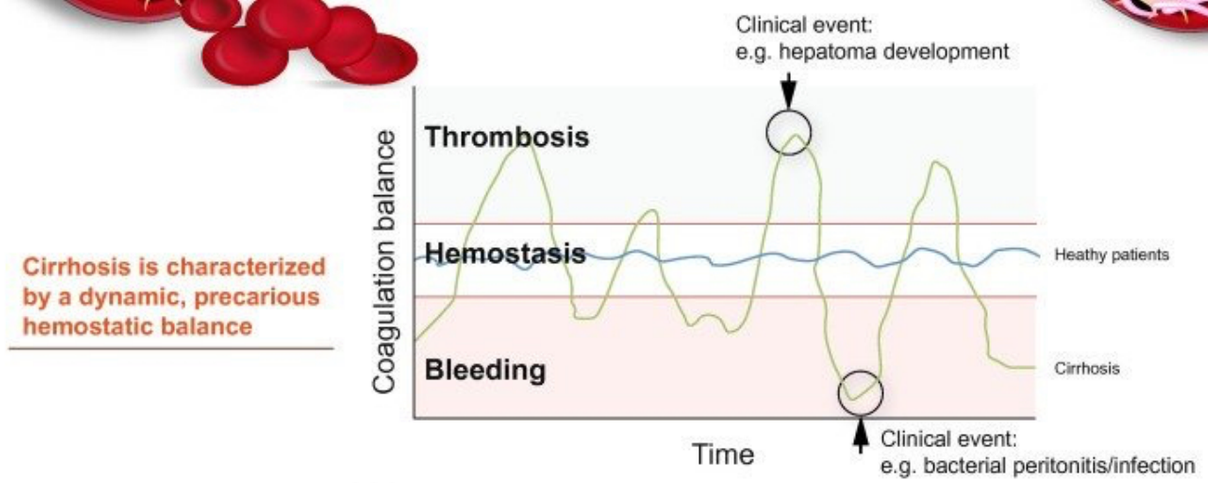
Hepatic Encephalopathy

OF - Cerebral

- Exclude other causes of Encephalopathy
- Generic Treatment: Lactulose/Rifaxamin
- PEG
- Don’t Protein restrict!!

Coagulation





Cirrhosis is characterized by a dynamic, precarious hemostatic balance

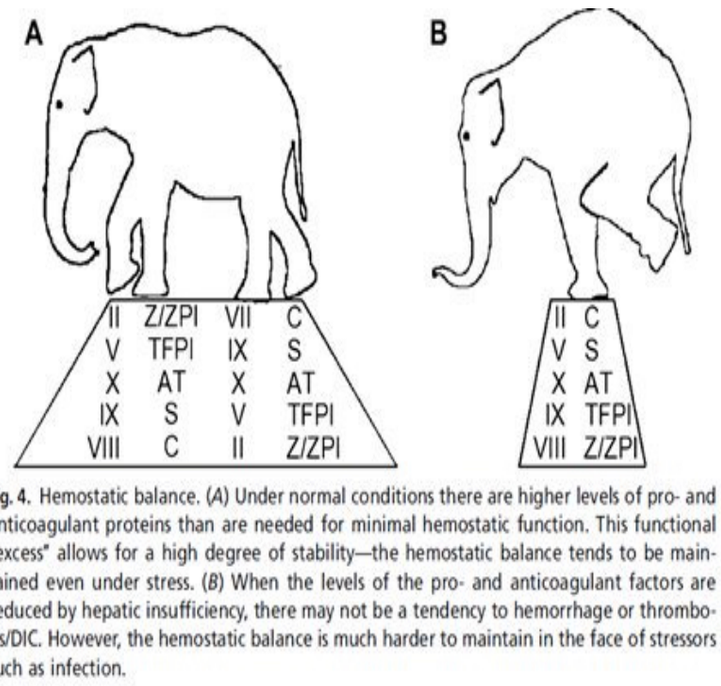


Fig. 4. Hemostatic balance. (*A*) Under normal conditions there are higher levels of pro- and anticoagulant proteins than are needed for minimal hemostatic function. This functional "excess" allows for a high degree of stability—the hemostatic balance tends to be maintained even under stress. (*B*) When the levels of the pro- and anticoagulant factors are reduced by hepatic insufficiency, there may not be a tendency to hemorrhage or thrombosis/DIC. However, the hemostatic balance is much harder to maintain in the face of stressors such as infection.

Clin Liver Dis 2009 Feb;13(1):1-9

Journal of Hepatology 2013 vol. 59 889–890

Treatment

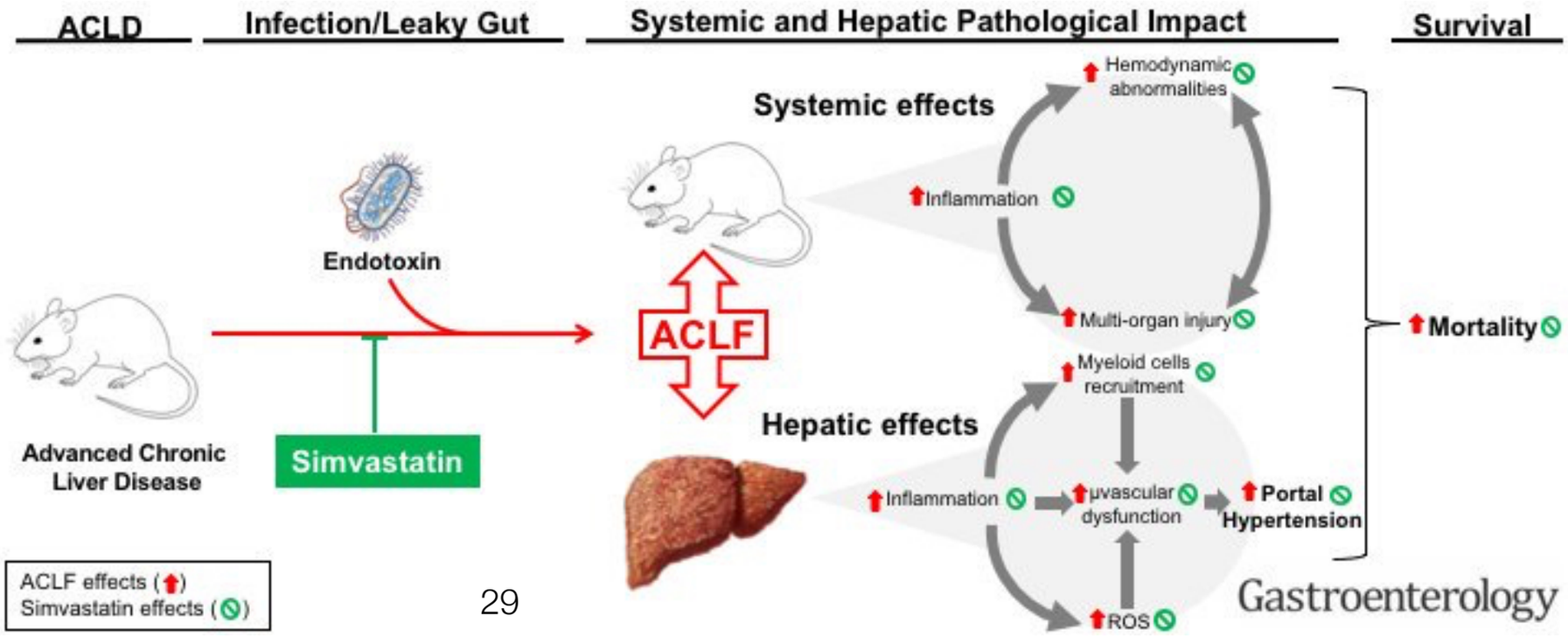
- The cause of liver injury can be treated in certain situations, e.g. HBV
- Early action is crucial to patient survival
  - Treatment of precipitating factors
  - Referral for LT before evolution of ACLF makes LT impossible

Recommendation		
Early identification and treatment of precipitating factors of ACLF, particularly bacterial infections, is recommended. However, in some patients ACLF progresses despite treatment of precipitating factors	III	1
Nucleoside analogues (tenofovir, entecavir) should be instituted as **early as possible i**n patients with HBV-related ACLF	I	1
Early referral of patients with ACLF **to LT centres** for immediate evaluation is recommended	II-3	1
Withdrawal of intensive care support after 1 week can be suggested in patients who are not LT candidates and have ≥4 organ failures	II-2	2
Administration of G-CSF cannot be recommended at present	I	2

EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024

Treatment

- Extracorporeal Support
  - MARS - Molecular Adsorbent Recirculating system
- Biological Support
- FMT
- Granulocyte Colony Stimulating Factor
- Statin

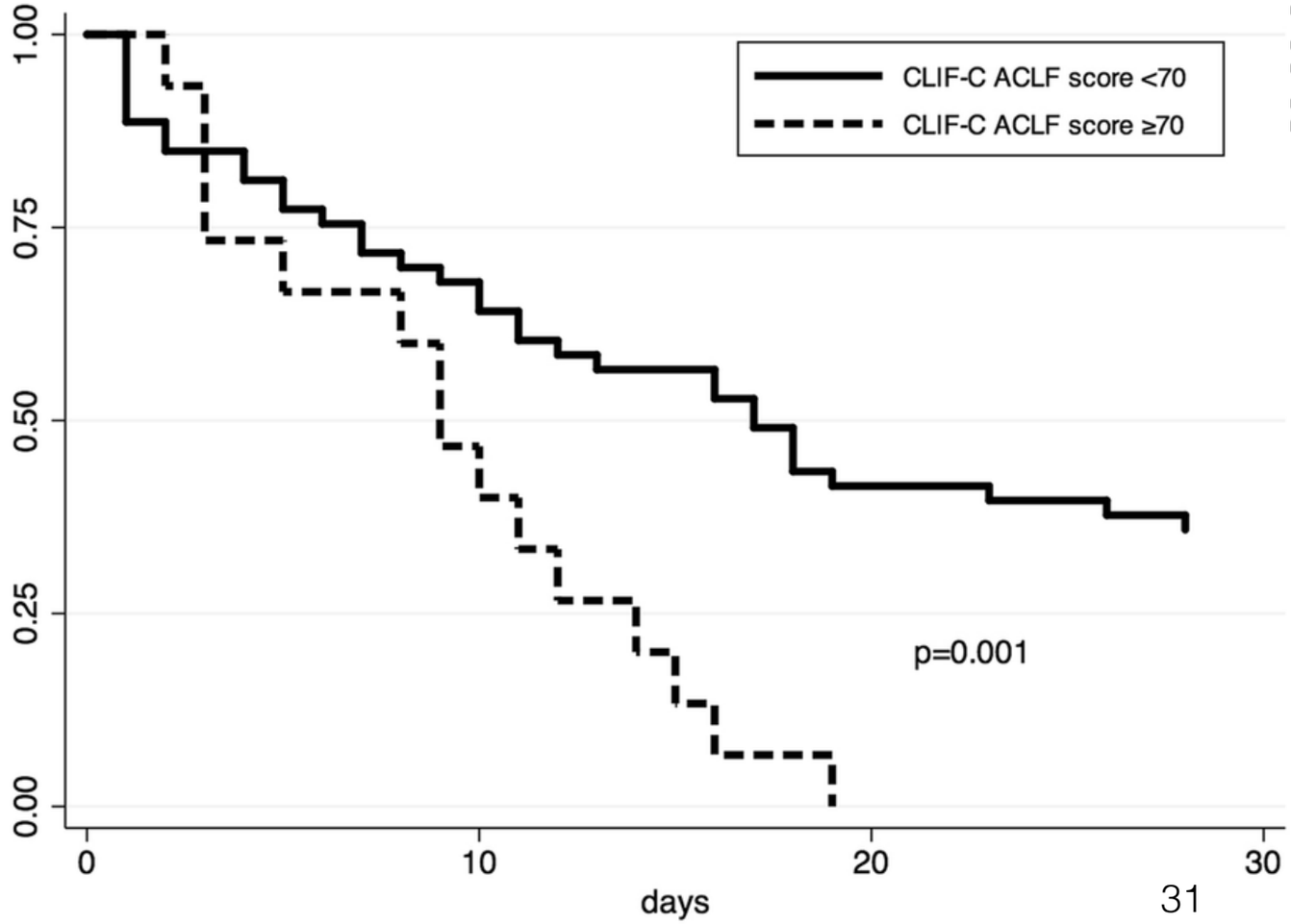


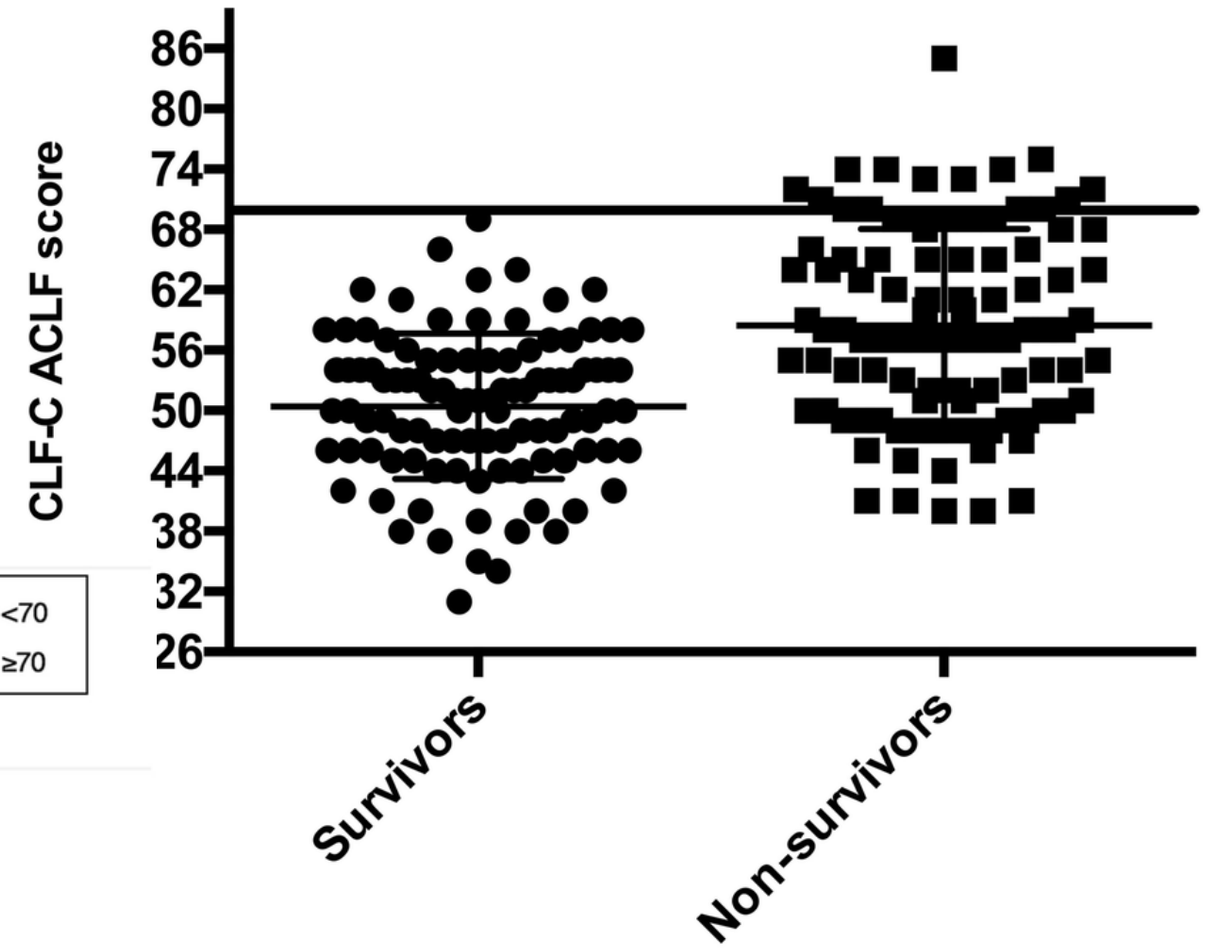
Futility in ACLF

- Futility
- Impact on donor pool
- CLIF-C ACLF Score **10*[0.33*CLIF-OFs+0.63(white cell count)-2]**

Futility

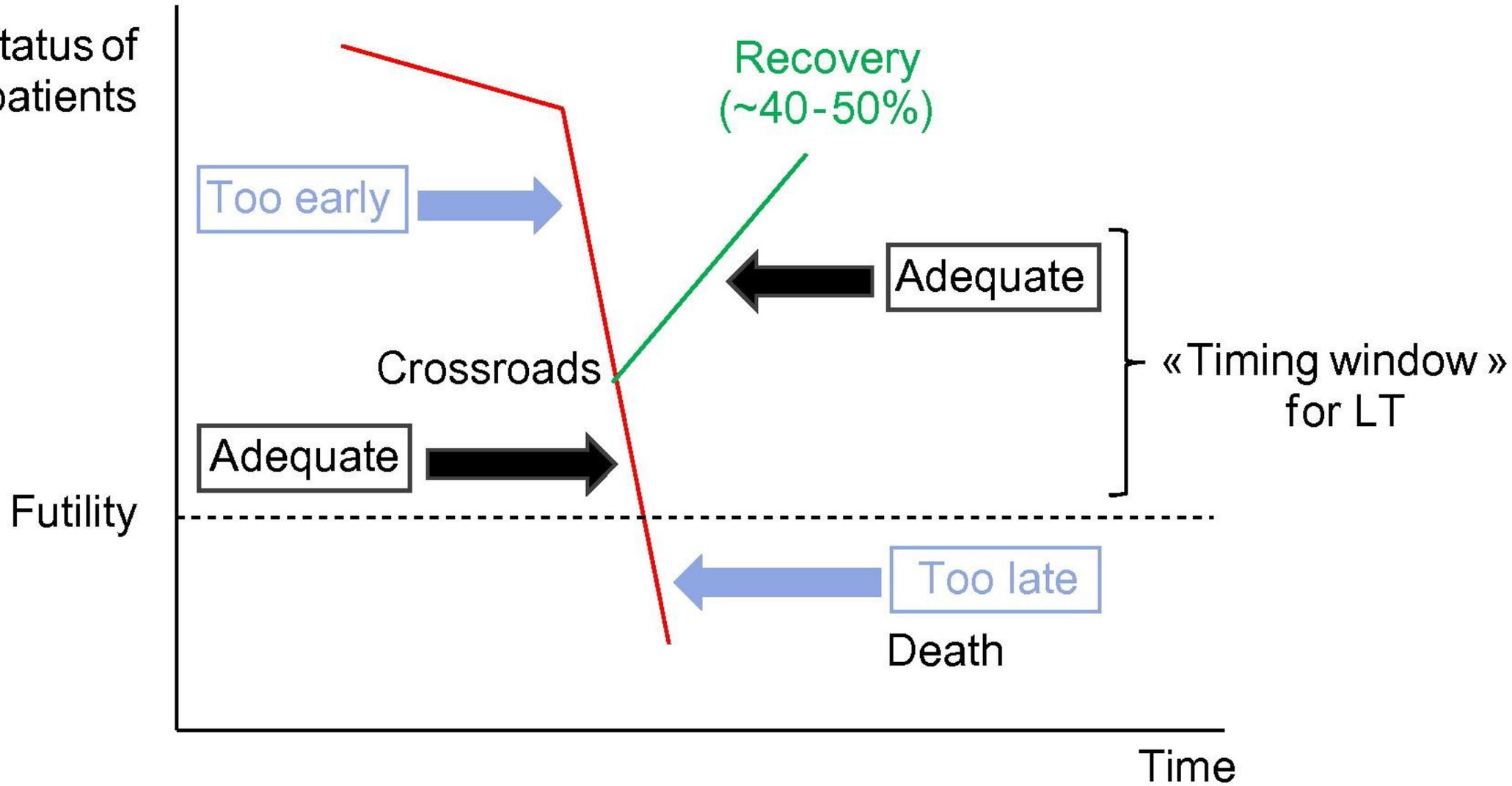
Twenty-eight-day survival according to the European Foundation for the study of chronic liver failure (CLIF-C) Acute-on-Chronic Liver Failure (ACLF) score in ACLF grade 3. Low 28-day survival is noted in patients with CLIF-C ACLF score ≥ 70, 2 days after receiving full intensive treatment unit supportive therapy





Engelmann et al. Critical Care (2018) 22:254

Transplant in ACLF



Journal of Hepatology **2018 69, 1384-1393**

ACLF-C CLIF Score

	DATA	SCORES
Bilirubin	1.7 mg/dl	Liver score 1 Liver failure ○ Yes ● No
Creatinine	20.4 mg/dl	Kidney score 3
Renal replacement therapy	● Yes ○ No	Renal failure ● Yes ○ No
West-Haven grade for HE	○ 0 ○ 1 ○ 2 ● 3 ○ 4	Brain score 3 Cerebral failure ● Yes ○ No
INR	1.8	Coagulation score 1 Coagulation failure ○ Yes ● No
MAP	65 mm/Hg	Circulation score 3
Use of vasopressors (Circulatory failure indication)	● Yes ○ No	Circulation failure ● Yes ○ No
Select one ● PaO_2 (preferred) ○ SpO_2	78	Lung score 3 Respiratory failure ● Yes ○ No
FiO_2	60 %	
Mechanical Ventilation	● Yes ○ No	
Reason for Mechanical Ventilation	Both	
		Total Number Failures 4 CLIF Organ Failure Score 14 **ACLF Grade** ACLF-Grade 3

10*[0.33*CLIF-OFs+0.63(white cell count)-2]

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

Probability of dying

DATA		SCORES	
Age	38 years		
White-cell count	1.9 10^9cells/L		
		CLIF-C ACLF Score	45
		Probability of dying at 1 month	18 %
		Probability of dying at 3 month	34 %
		Probability of dying at 6 month	39 %
		Probability of dying at 12 month	47 %

Reset Compute

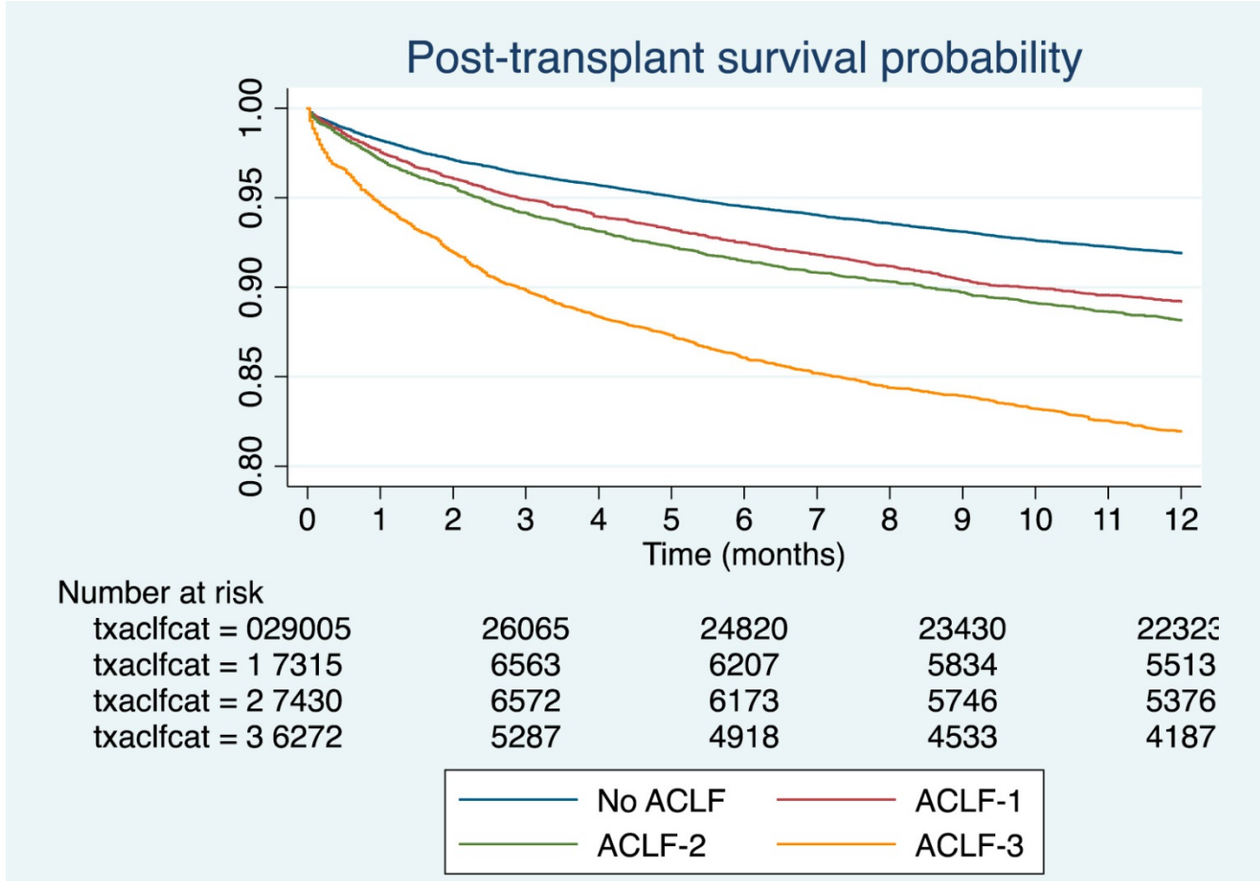
https://www.clifresearch.com/ToolsCalculators.aspx

Is Salvage Liver Transplant an option?

- Active Infection
- Active Drinking
- Multiple organs failing

CLIF-C ACLF Score	45
Probability of dying at 1 month	18 %
Probability of dying at 3 month	34 %
Probability of dying at 6 month	39 %
Probability of dying at 12 month	47 %

Survival with ACLF Grade



***Gastroenterology* 2019 156, 1381-1391.e3**

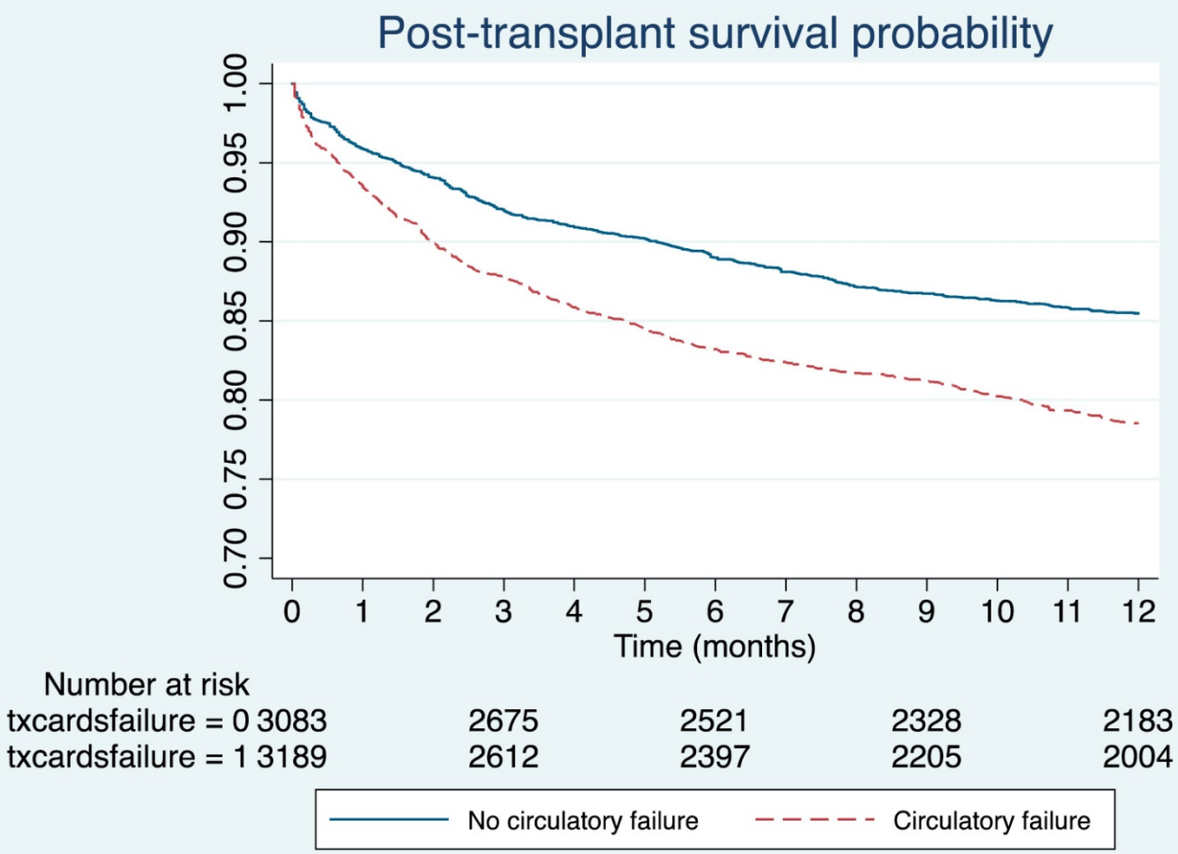
Gastroenterology
Volume 156, Issue 5, April 2019, Pages 1381-1391.e3

Original Research
Full Report: Clinical—Liver

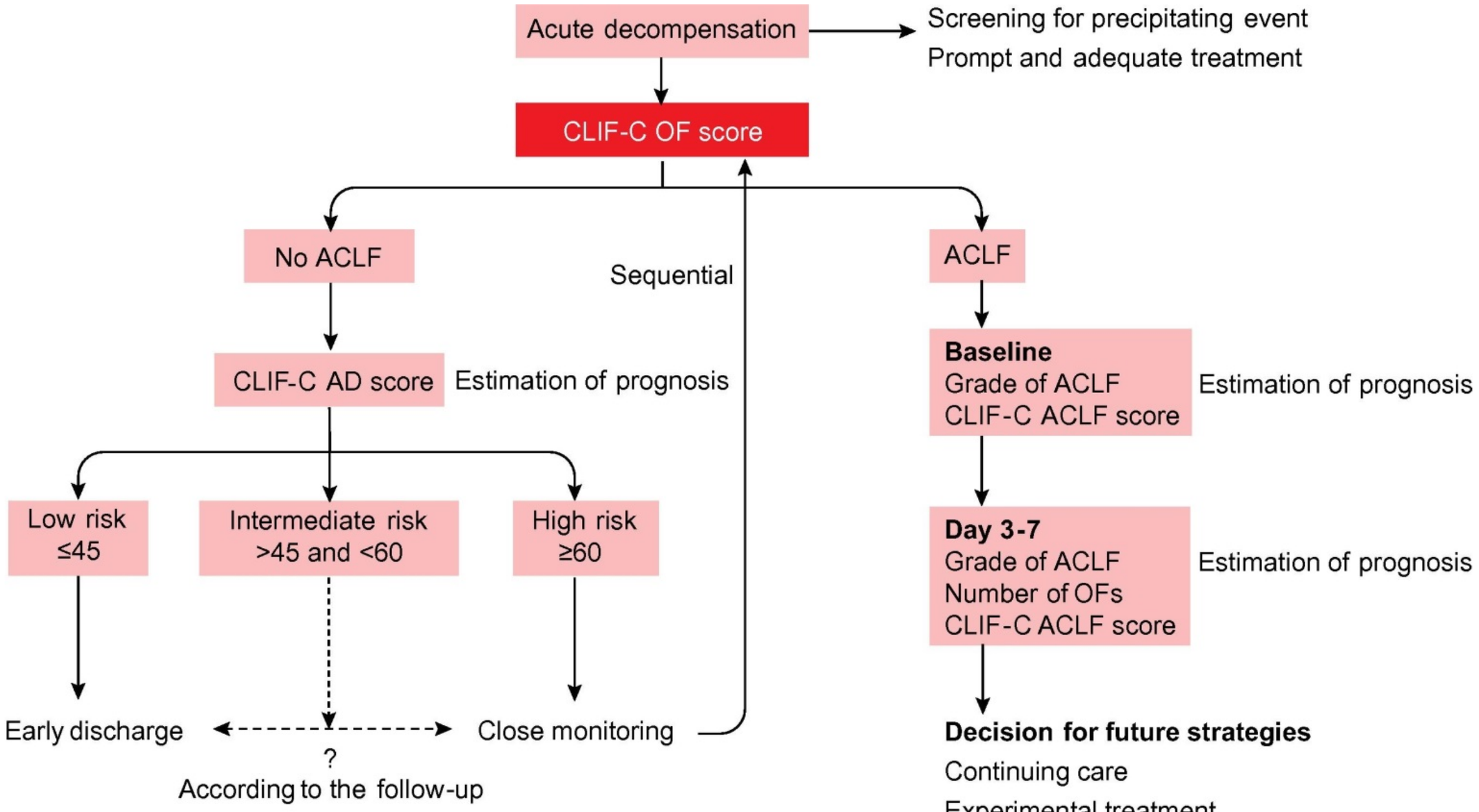
Factors Associated with Survival of Patients With Severe Acute-On-Chronic Liver Failure Before and After Liver Transplantation

Vinay Sundaram [1,*], Rajiv Jalan [2,*], Tiffany Wu [3], Michael L. Volk [4], Sumeet K. Asrani [5], Andrew S. Klein [6], Robert J. Wong [7]

Survival with Circulatory failure



Conclusion



***Journal of Hepatology* 2018 69, 1384-1393**

Acute on Chronic Liver failure

Wits University Donald Gordon Medical Centre

Patient-centred. Independent. Academic.

MEDICLINIC

WITS TRANSPLANT

Progressive medicine, exceptional care.

Liver Unit: 0113566488/6507
bilalbobat@mweb.co.za