

# Acute-on-Chronic Liver Failure (ACLF): Current status and recent advances

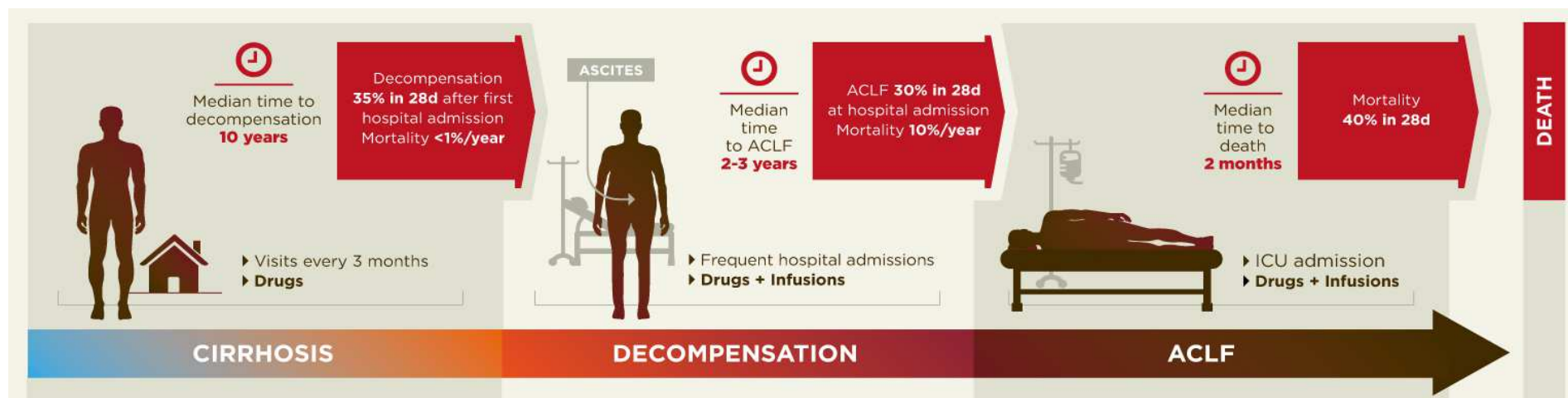
**Prof. Dr. med. Jonel Trebicka, PhD**

Translational Hepatology, Department of Internal Medicine I, Goethe University Frankfurt

European Foundation for Study of Chronic Liver Failure, EF-CLIF, Barcelona



# Natural history of liver cirrhosis

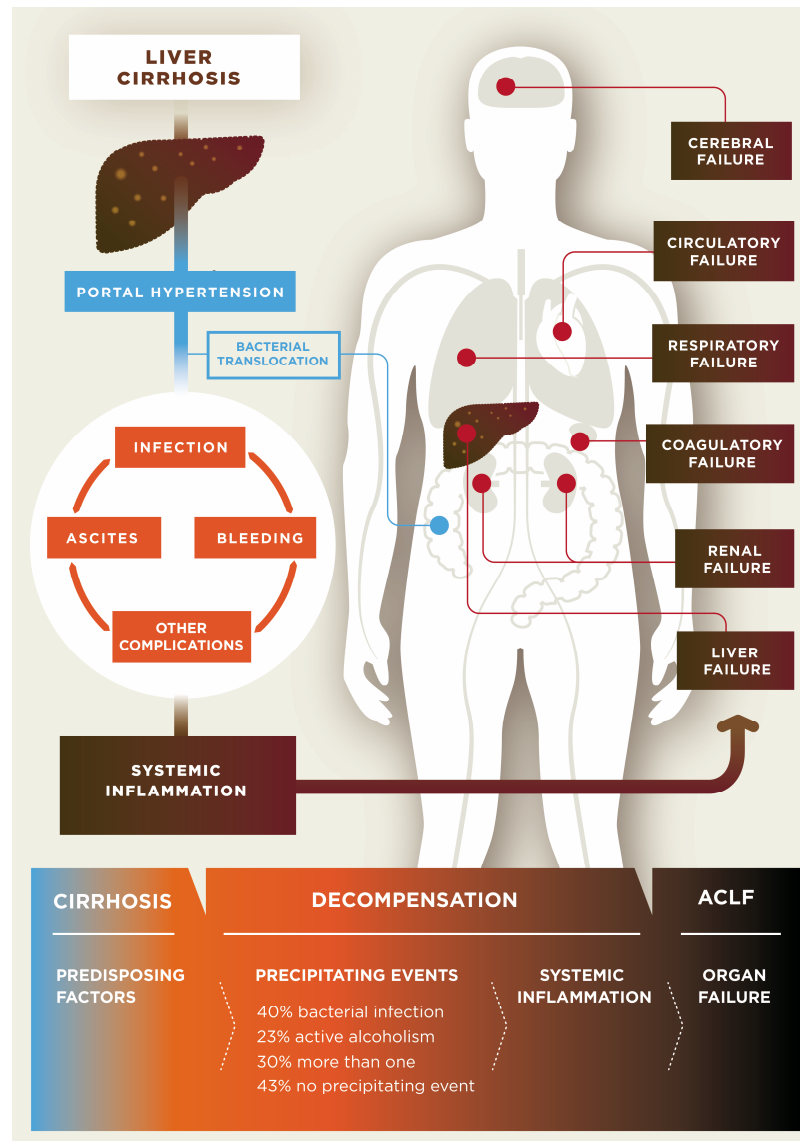


**Acute-on-Chronic Liver failure (ACLF)** is defined as a syndrome occurring in cirrhosis, characterized by

- acute decompensation [acute development of ascites, overt encephalopathy, GI-hemorrhage, new onset of non-obstructive jaundice and/or bacterial infections],
- the development of organ failure(s) and
- high short-term mortality.

# Agenda

- Diagnosis, grading
- Development, precipitants
- Clinical course
- Pathogenesis
- Management, prevention



**MICROB-PREDICT**

Trebicka, Reberger, Laleman. Visc Med 2018



# Diagnosis and Grading



# Diagnosis and grades of ACLF MICROB-PREDICT

The diagnosis and the grading of ACLF is based on the assessment of organ function as defined by the CLIF-C OF score.

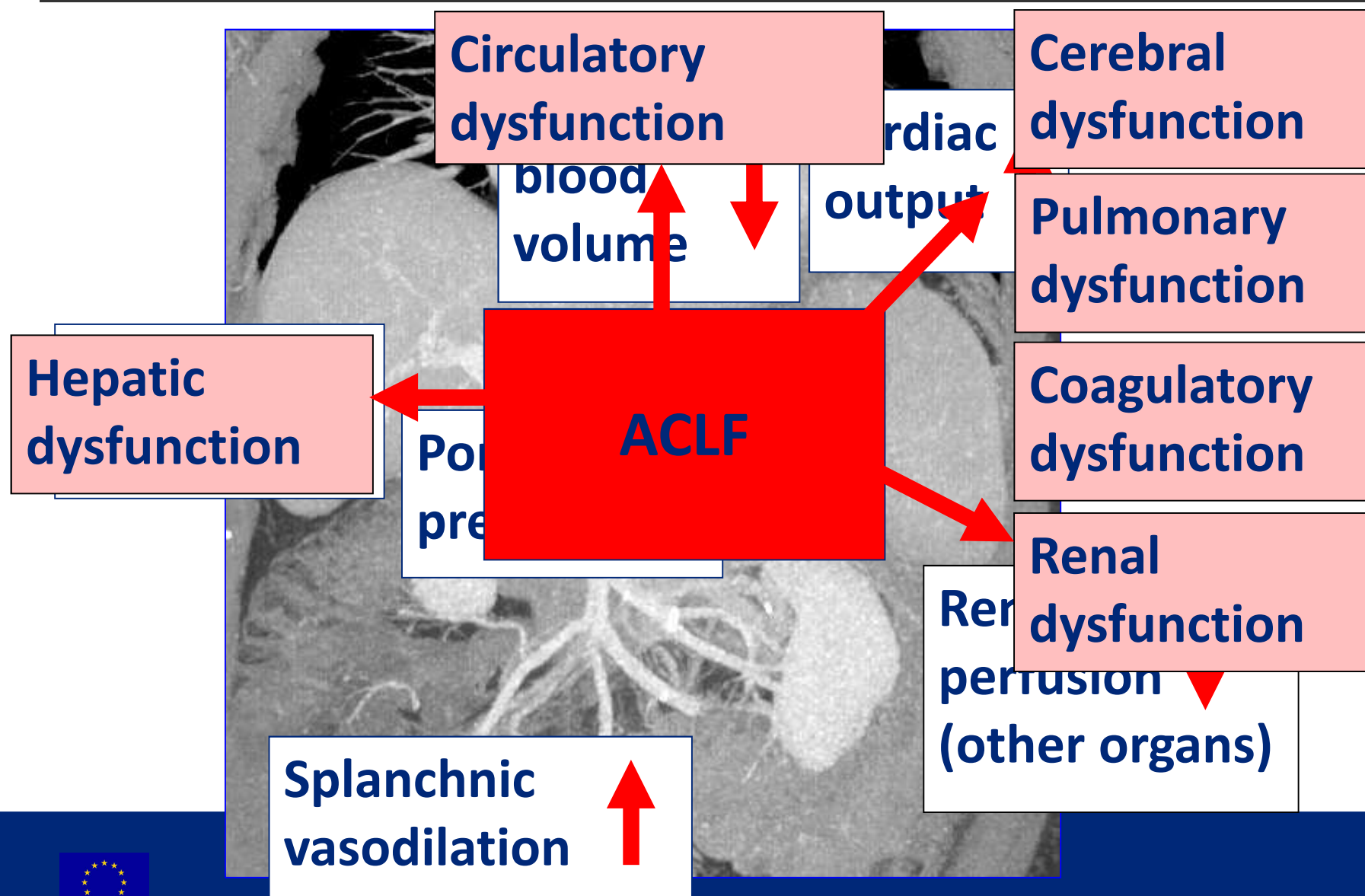
	TX-free patients ( <i>n</i> = 1,287)	28-d mortality rate	ACLF grades
No organ failure	879 (68.3%)	39/879 (4.4%)	→ No ACLF
Single nonrenal failure, creatinine < 1.5 mg/dL, no HE	128 (9.9%)	8/128 (6.3%)	
Single renal failure	86 (6.7%)	16/86 (18.6%)	→ ACLF-1
Single nonrenal failure, creatinine 1.5–1.9 mg/dL and/or HE	54 (4.1%)	15/54 (27.7%)	
2 organ failures	97 (7.5%)	31/97 (32.0%)	→ ACLF-2
3 organ failures	25 (1.9%)	17/25 (68.0%)	→ ACLF-3
4–6 organ failures	18 (1.4%)	12/18 (88.9%)	



# Development



# Development of ACLF in decompensated liver cirrhosis



# Precipitating events



**Table 1. Characteristics of patients with or without ACLF.**

Characteristic	No ACLF <sup>a</sup> (N = 871)	ACLF (N = 417)	<i>p</i> value
Age (yr)	58.1 ± 12.3	55.8 ± 11.7	0.0011
Male sex	551 (63.3)	267 (64.0)	0.7887
Ascites	533 (61.4)	289 (80.7)	<0.001
Mean arterial pressure (mmHg)	84.8 ± 11.9	78.4 ± 13.1	<0.001
Cause of cirrhosis			
Alcohol	398 (48.5)	233 (58.4)	0.0011
Hepatitis C virus	182 (22.2)	59 (14.8)	0.0024
Alcohol plus hepatitis C virus	76 (9.3)	37 (9.3)	0.9927
Potential precipitating events of ACLF			
Bacterial infection	218 (25.2)	160 (39.1)	<0.001
Gastrointestinal hemorrhage	99 (15.6)	74 (17.8)	0.3505
Active alcoholism within the last 3 months <sup>b</sup>	115 (13.9)	89 (22.9)	<0.001
Other precipitating event <sup>c</sup>	31 (3.8)	38 (9.6)	<0.001
No precipitating event <sup>d</sup>	483 (64.8)	124 (43.1)	<0.001
More than one precipitating event <sup>e</sup>	41 (28.7)	25 (29.8)	0.8613

## CANONIC-study

**40% bacterial infection**

**23% active alcoholism**

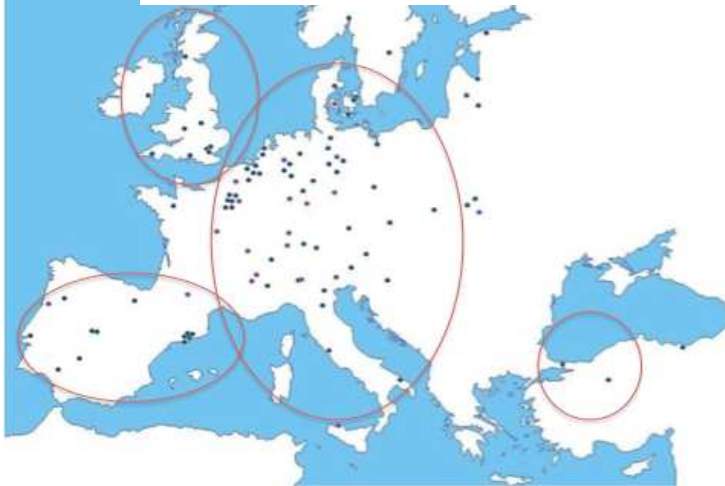
**30% more than one**

**43% no precipitating event**

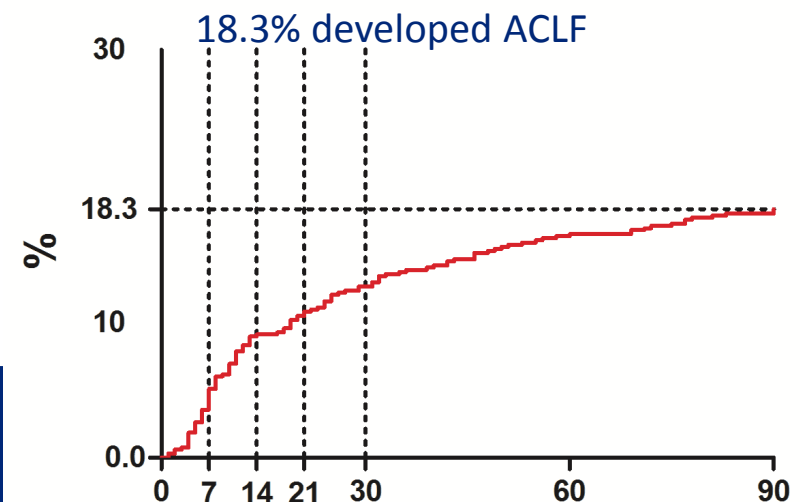
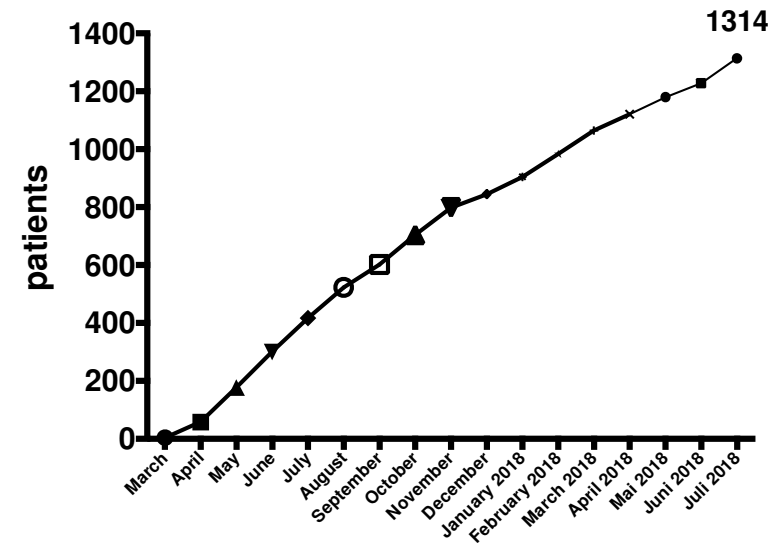
Jalan et al. J Hepatol 2011



53 centers applied to participate  
48 initiated  
47 at least one patient



### Recruitment in PREDICT



# Clinical Course

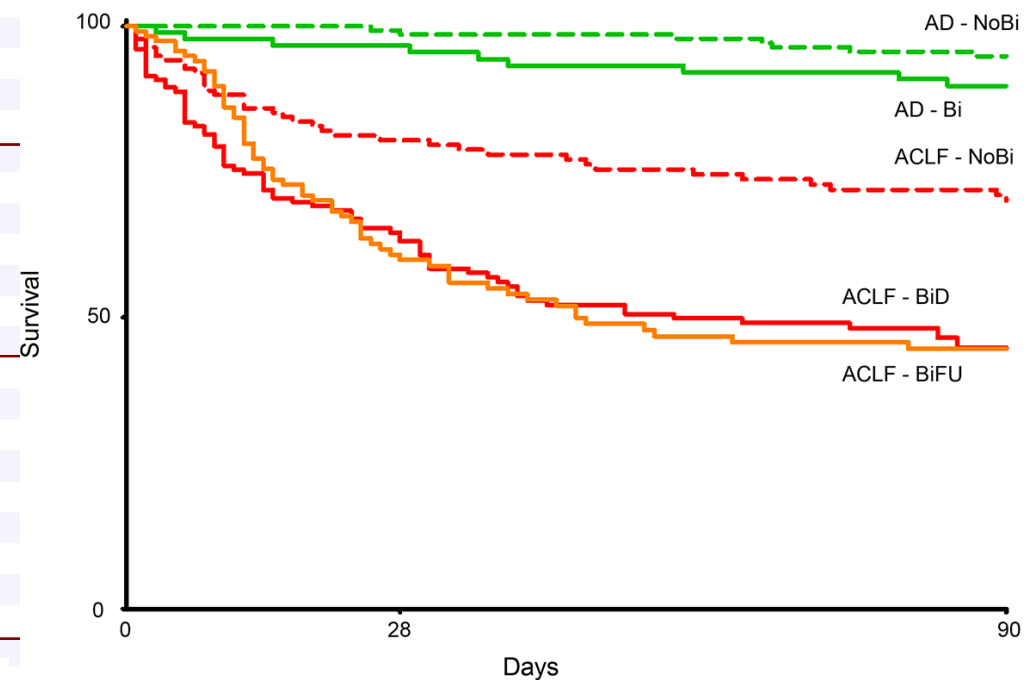


# Clinical features

Table 1. Characteristics of patients with or without ACLF.

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No precipitating event <sup>d</sup>	483 (64.8)		
More than one precipitating event <sup>e</sup>	41 (28.7)		
Organ failures			
Liver	51 (7.9)		
Kidney	0 (0)		
Cerebral	13 (2.0)		
Coagulation	14 (2.2)		
Circulation	10 (1.6)		
Lungs	3 (0.5)		
Kidney dysfunction <sup>f</sup>	68 (7.8)		
Mild-to-moderate hepatic encephalopathy <sup>g</sup>	221 (25.4)		

**A**



**Younger**  
**More ascites**  
**More alcoholic cirrhosis**  
**More organ failure**

**Bacterial infections precipitating and complicating ACLF**

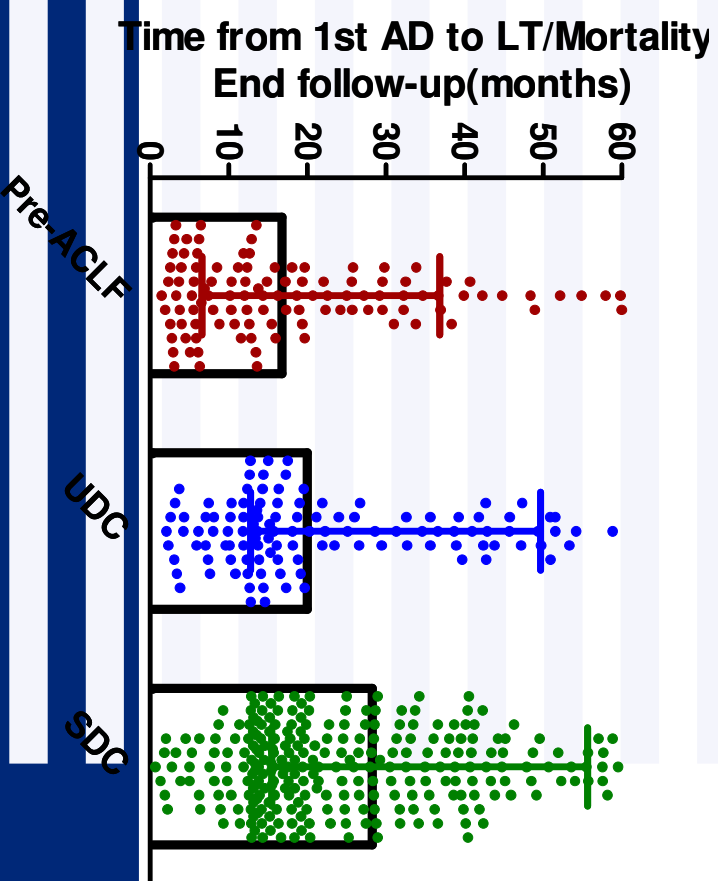
# Role of previous decompensation

OB-PREDICT

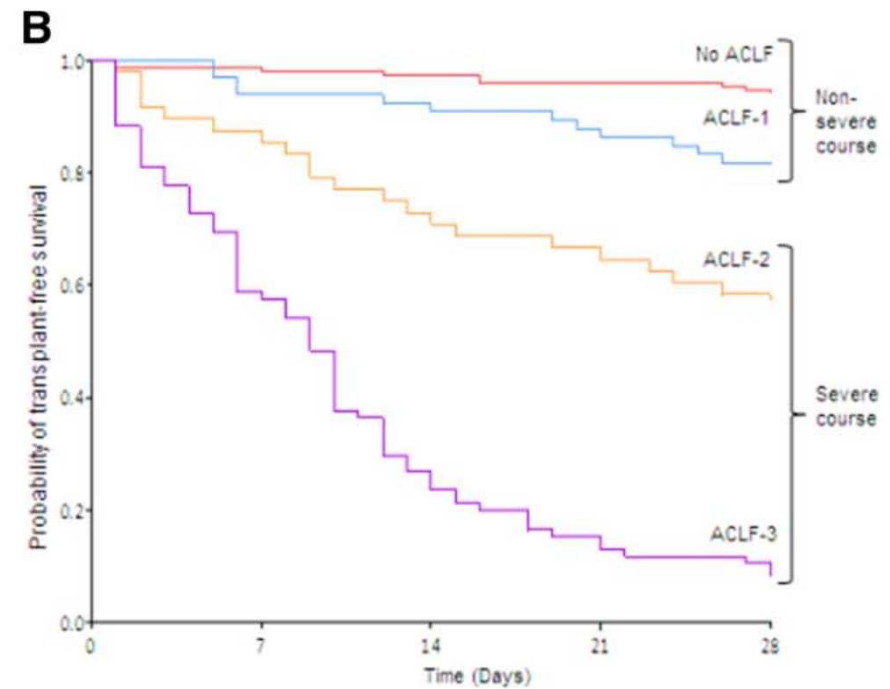
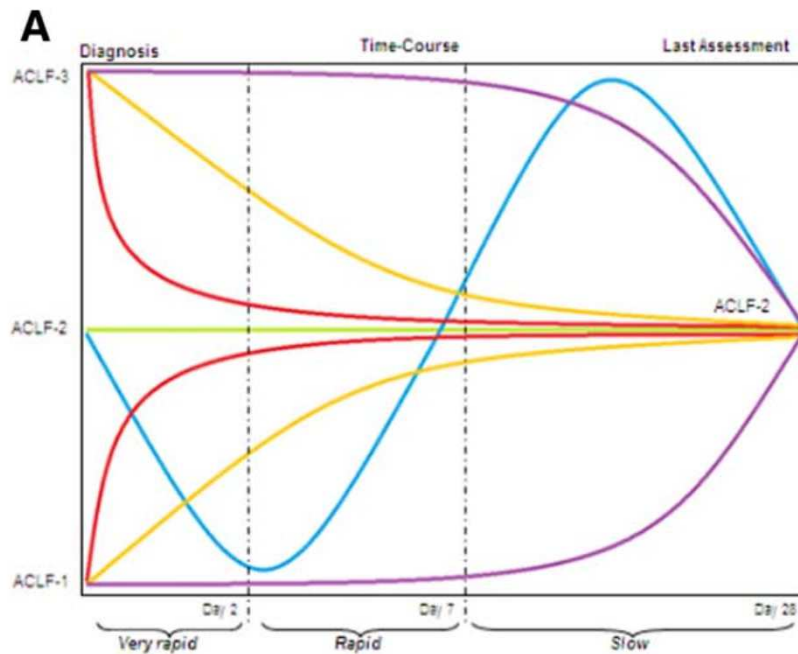
Table 1. Characteristics of patients with or without ACLF.

Characteristic	No ACLF <sup>a</sup> (N = 871)	ACLF (N = 417)	p value
Time from first previous decompensation			
Less than 3 months	507 (58.2)	50 (12.0)	0.0000
From 3 to 49 months	400 (45.9)	60 (14.3)	0.0967
More than 49 months	64 (7.4)	107 (25.7)	

Moreau et al. Gastroenterology 2013



# Dynamic clinical course of ACLF



# Pathogenesis

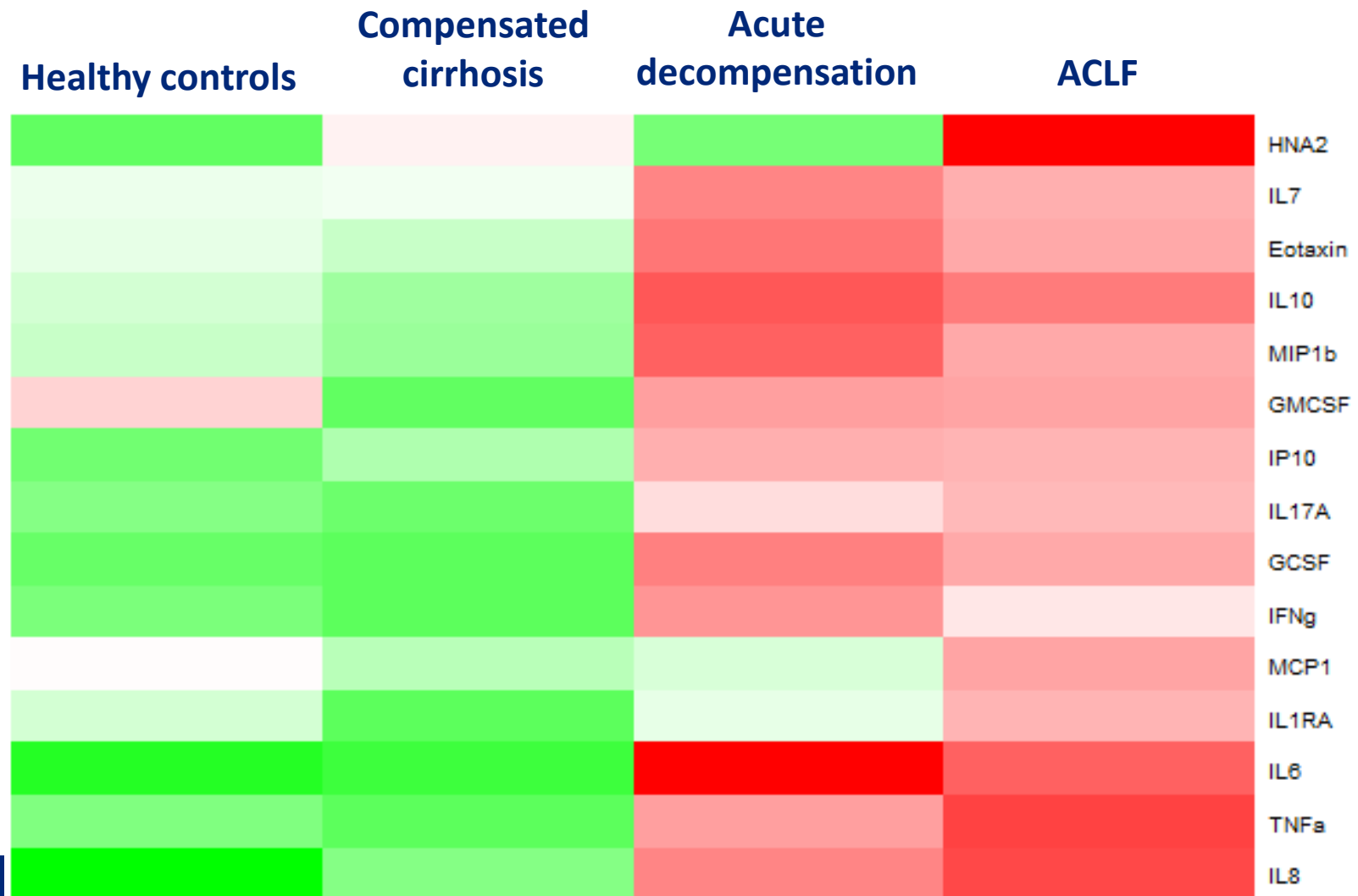


# Systemic inflammation



	Healthy controls (n=40)	No ACLF (n=285)	ACLF (n=237)	p-value*
<b><i>Pro-inflammatory Cytokines</i></b>				
TNF $\alpha$ (pg/ml)	9(7-12)	20(14-27)	29(17-41)	<0.001
IL-6 (pg/ml)	0.3(0.3-0.3)	21(11-41)	39(17-115)	<0.001
IL-8 (pg/ml)	1.6(0.6-3.3)	37(20-76)	84(41-169)	<0.001
MCP-1 (pg/ml)	37(21-41)	318(228-436)	410(288-713)	<0.001
<b><i>Anti-inflammatory Cytokines</i></b>				
IL-10 (pg/ml)	1.1(0.4-1.1)	3.4(1.1-9.2)	8.1(2.1-29.9)	<0.001
IL-1ra (pg/ml)	7(3-9)	10(5-22)	23(9-63)	<0.001
<b><i>Other Cytokines</i></b>				
IFN $\gamma$ (pg/ml)	0.8(0.8-4.9)	6(2-18)	7(3-24)	0.044
IFN $\alpha$ 2 (pg/ml)	3(3-3)	22 (8-56)	27 (11-63)	0.113
IL-17a (pg/ml)	0.7(0.7-2.7)	3.7(1.6-10.3)	4.5(1.6-15.6)	0.128

# Extent of systemic inflammation in cirrhosis





# Extensive systemic inflammation leads to ACLF

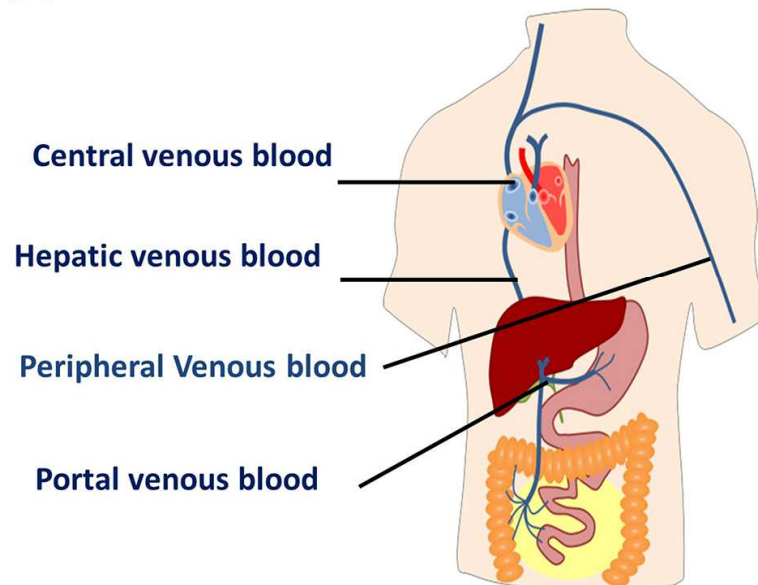


**Which is the trigger of  
systemic inflammation?**

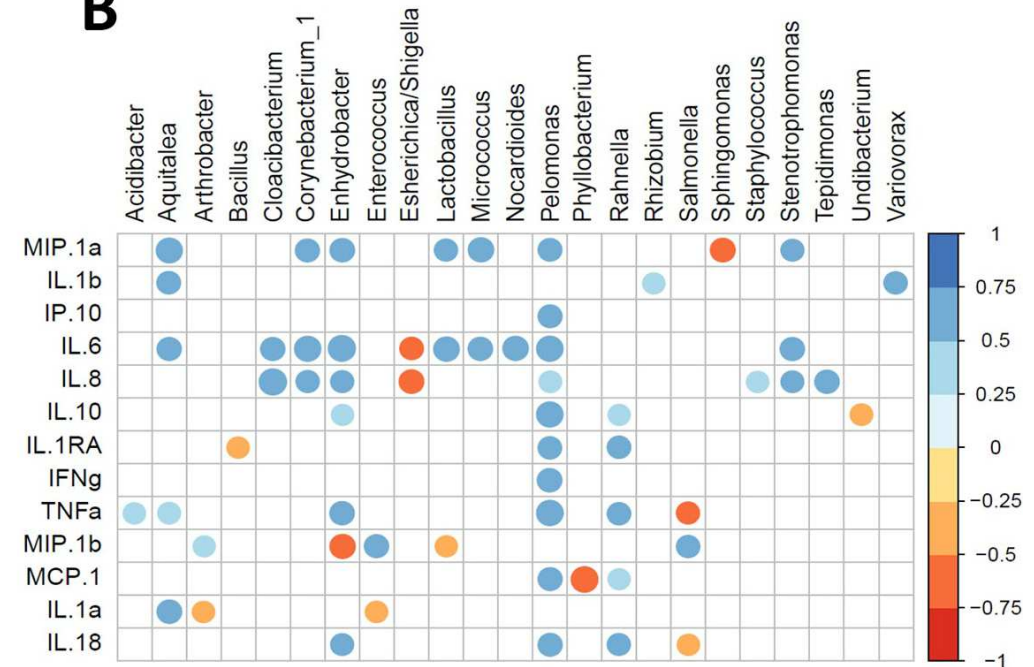


# Circulating microbiome associated with systemic inflammation

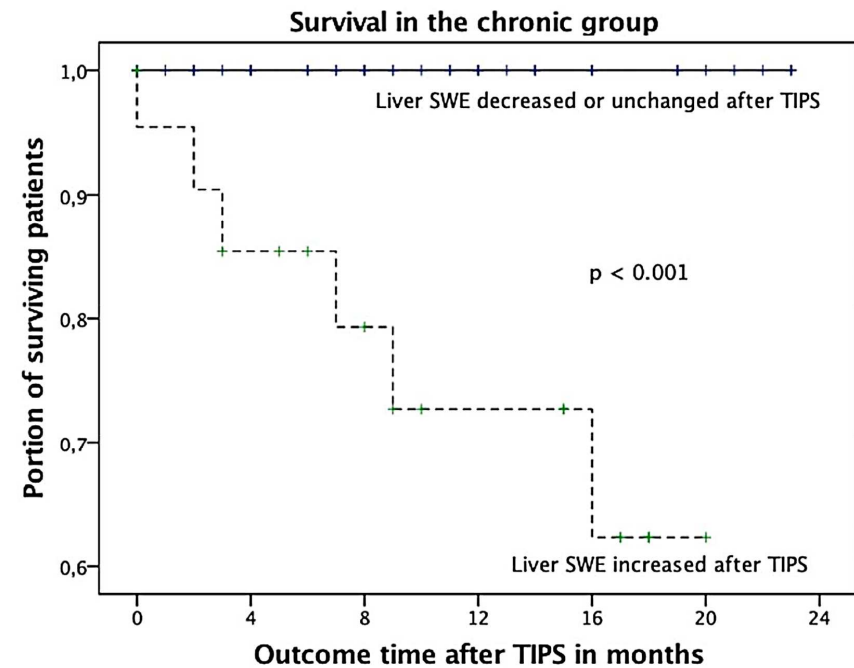
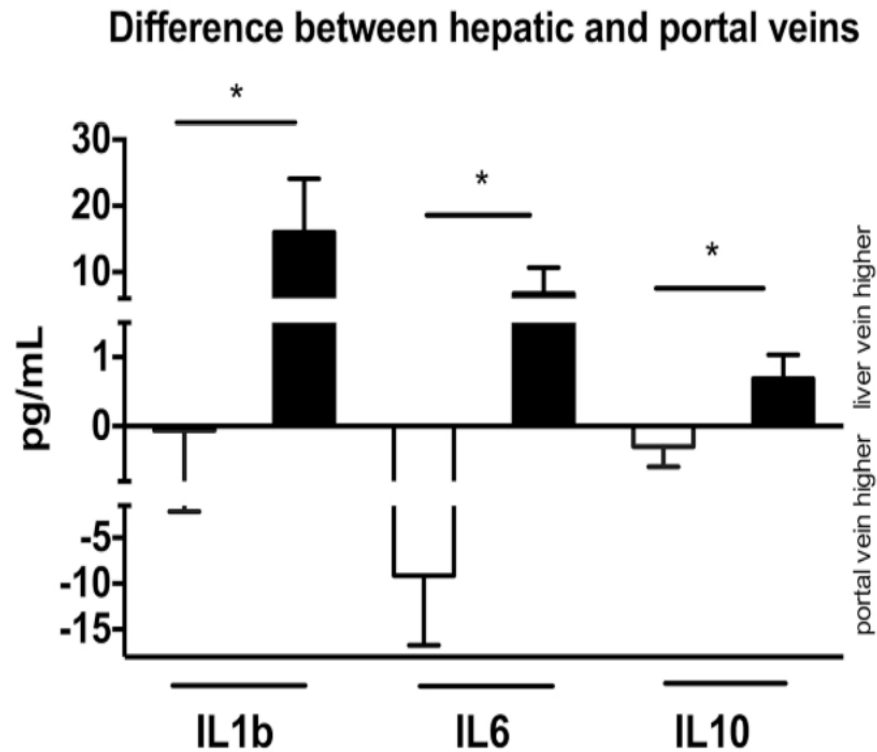
**A**



**B**



# Many inflammatory markers derive from the liver

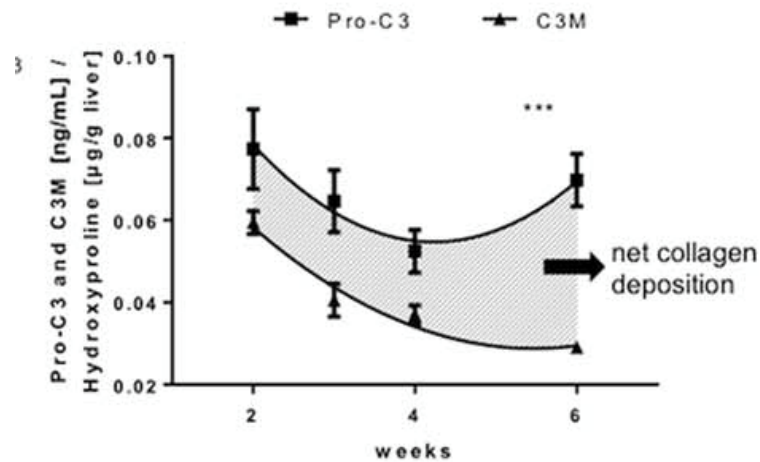


# Effect of systemic inflammation?

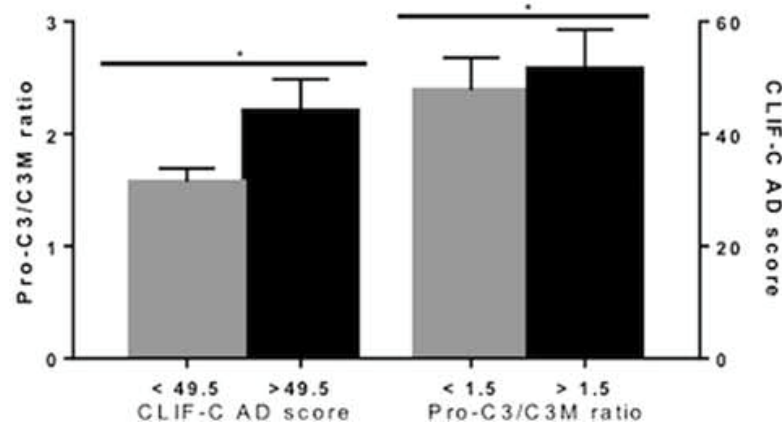


# Systemic inflammation induces hepatic collagen accumulation and cell death

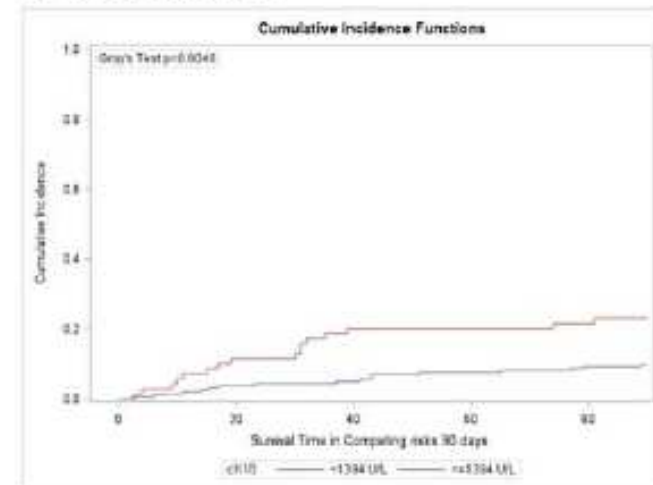
**C** time course of collagen type 3 markers normalized for hepatic hydroxyproline content



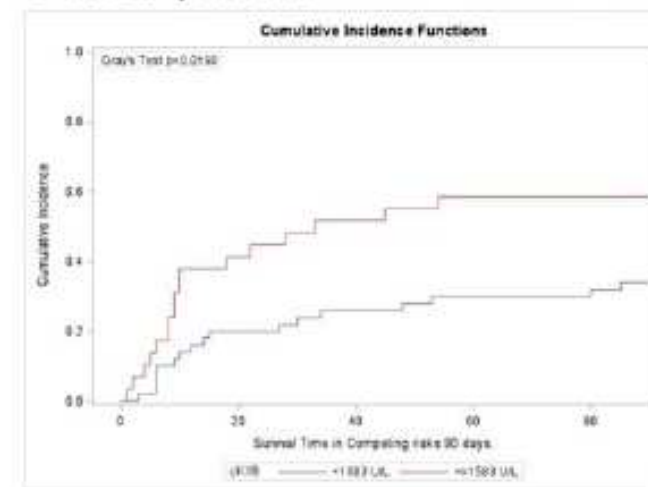
Relationship of Pro-C3/C3M ratio and CLIF-C AD score



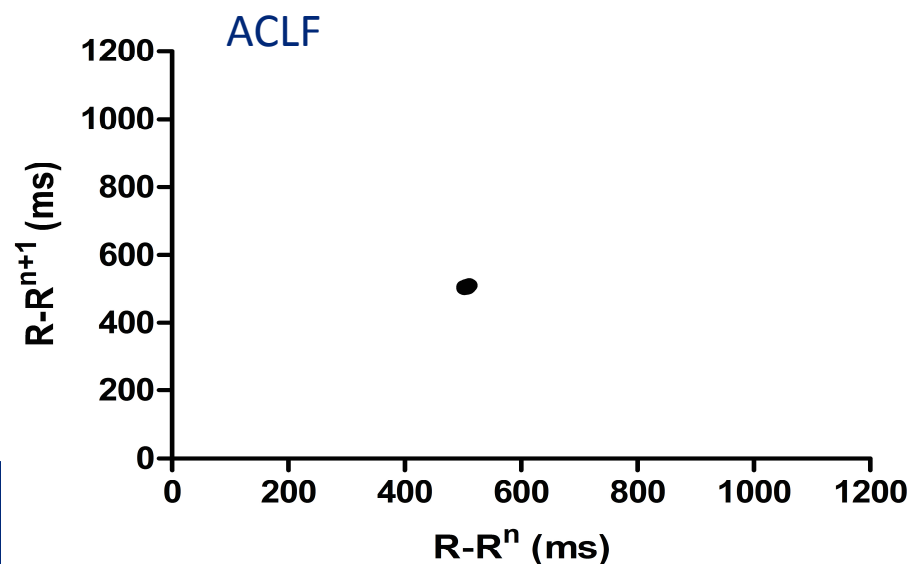
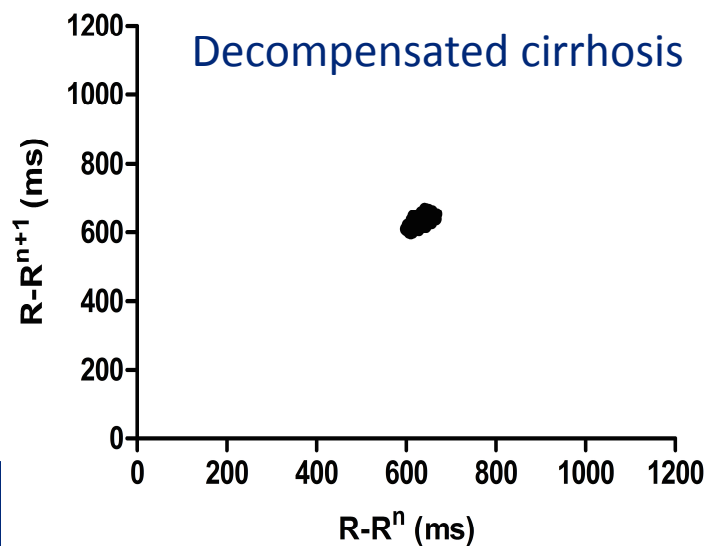
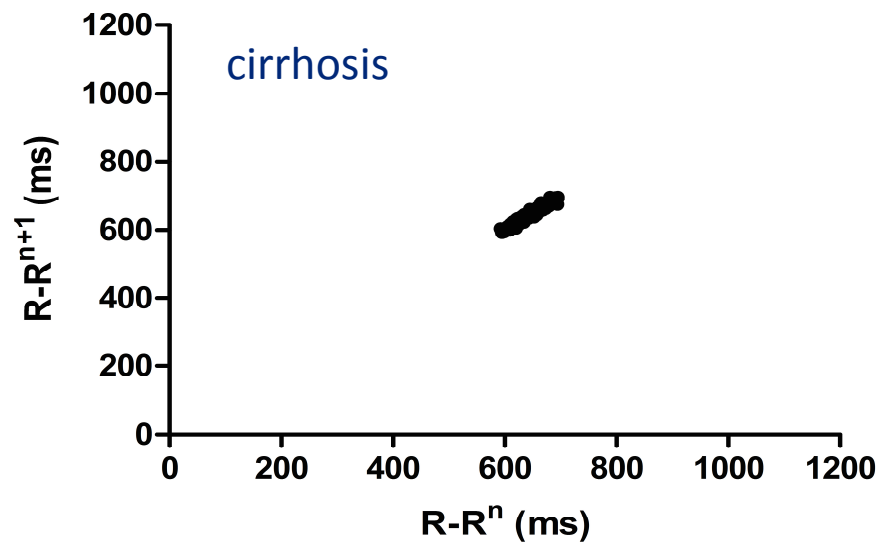
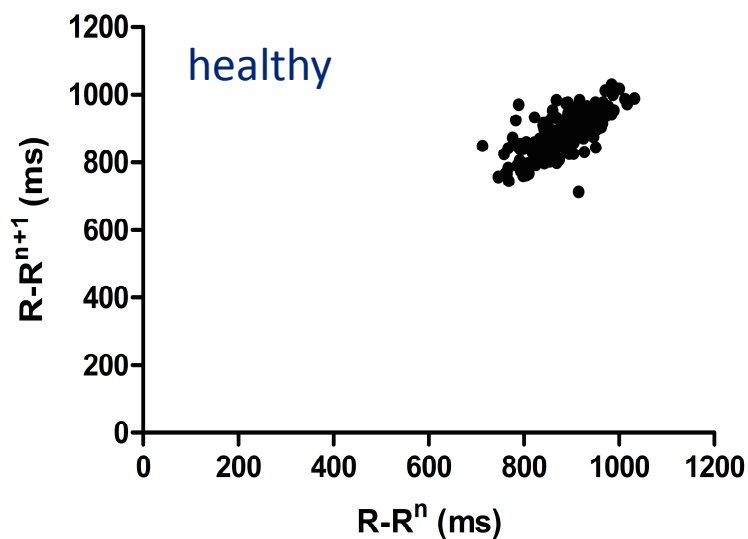
**A** AD patients



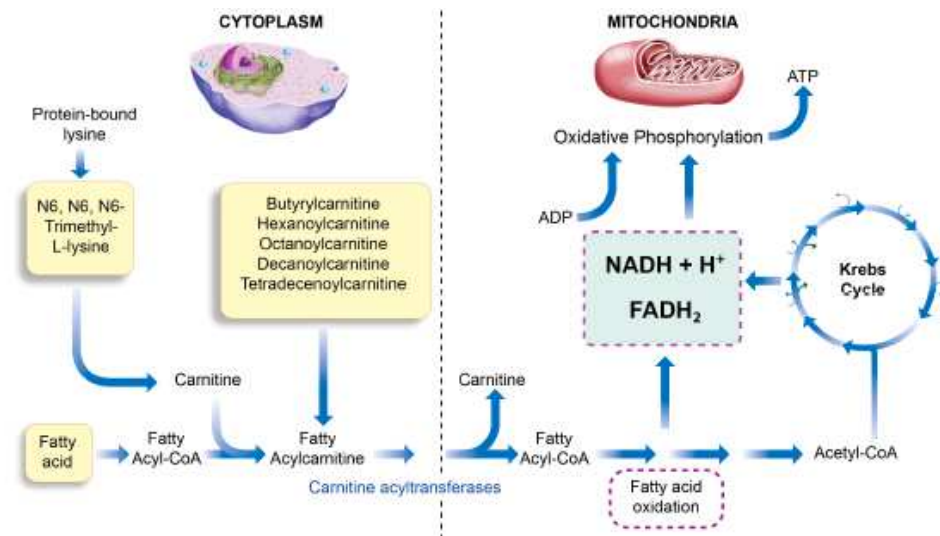
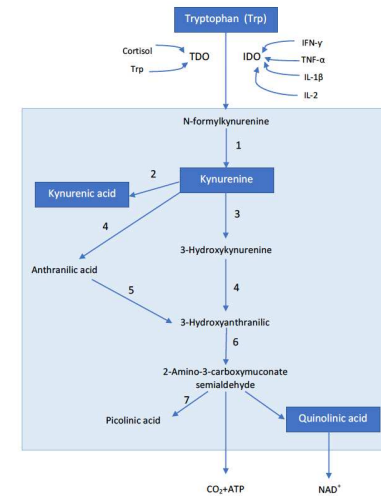
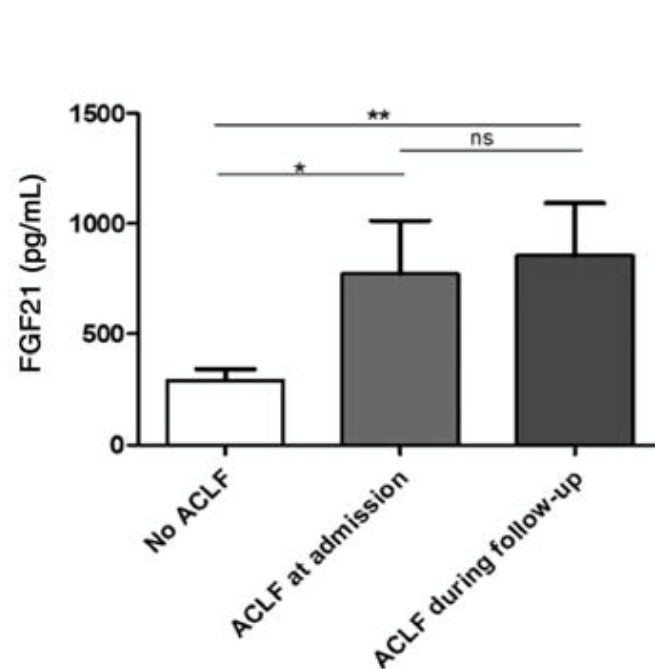
**B** ACLF patients



# Heart rate variability and ACLF



# Metabolomics data suggest an energetic crisis

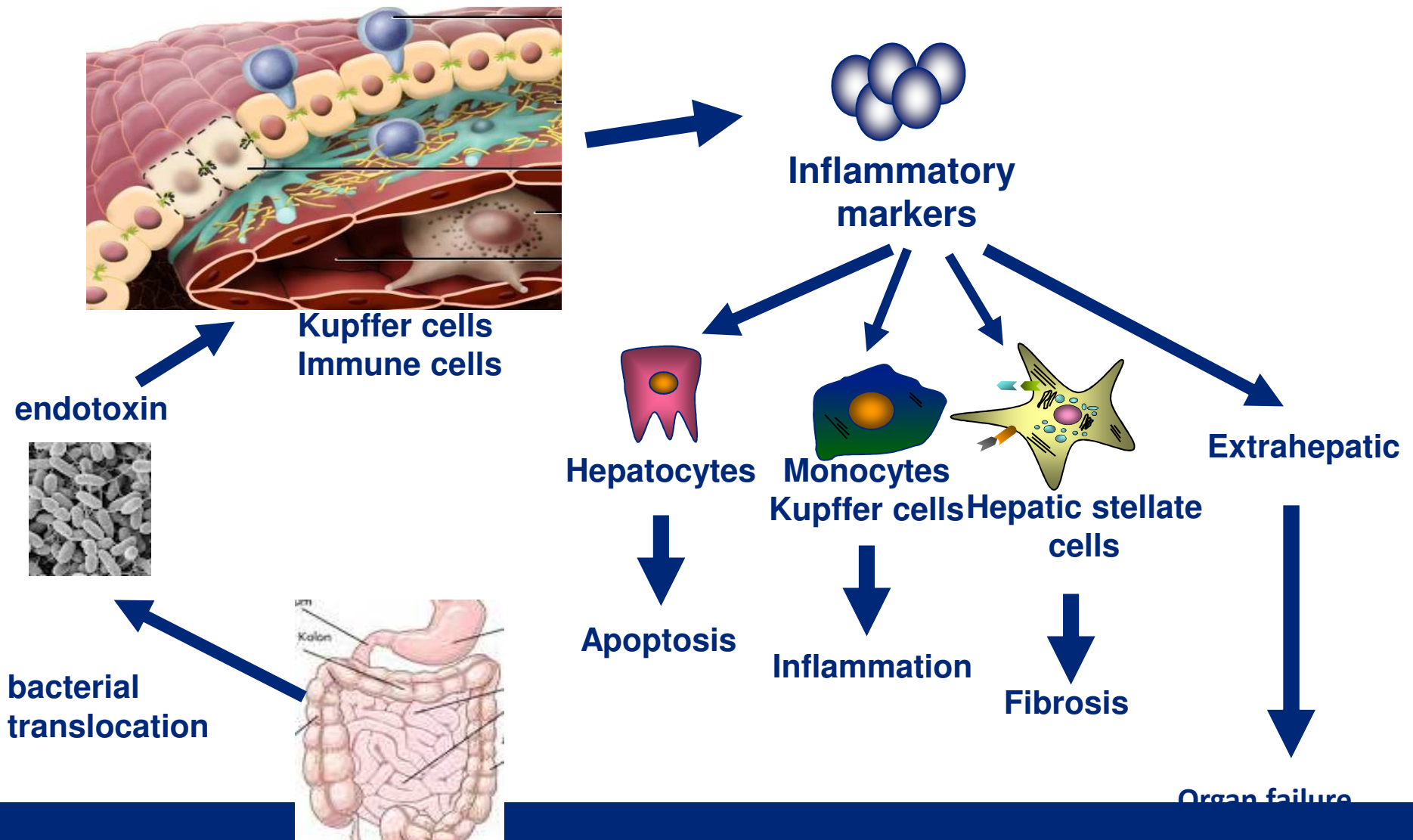


Ruiz-Margain et al. Liver Transplantation 2018  
 Claria, et al. Hepatology 2018  
 Moreau et al. J Hepatol 2019





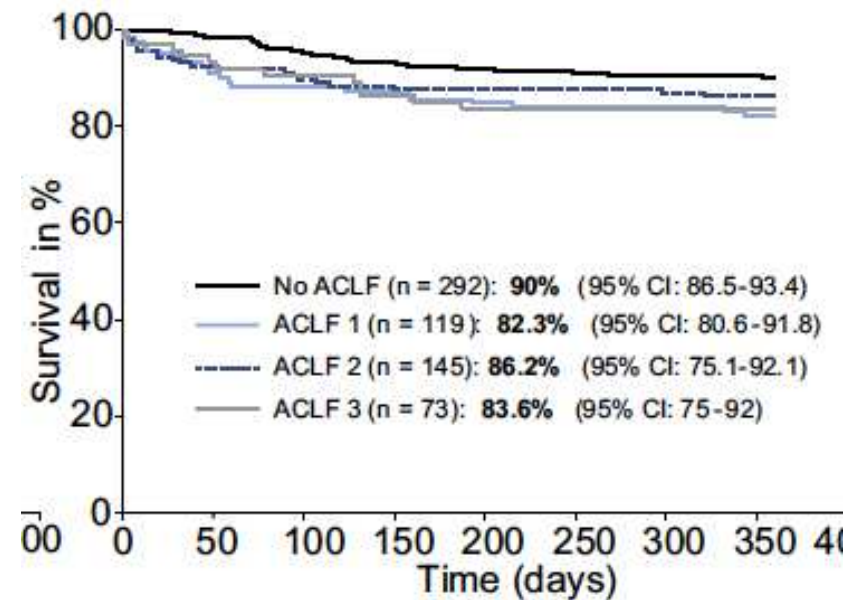
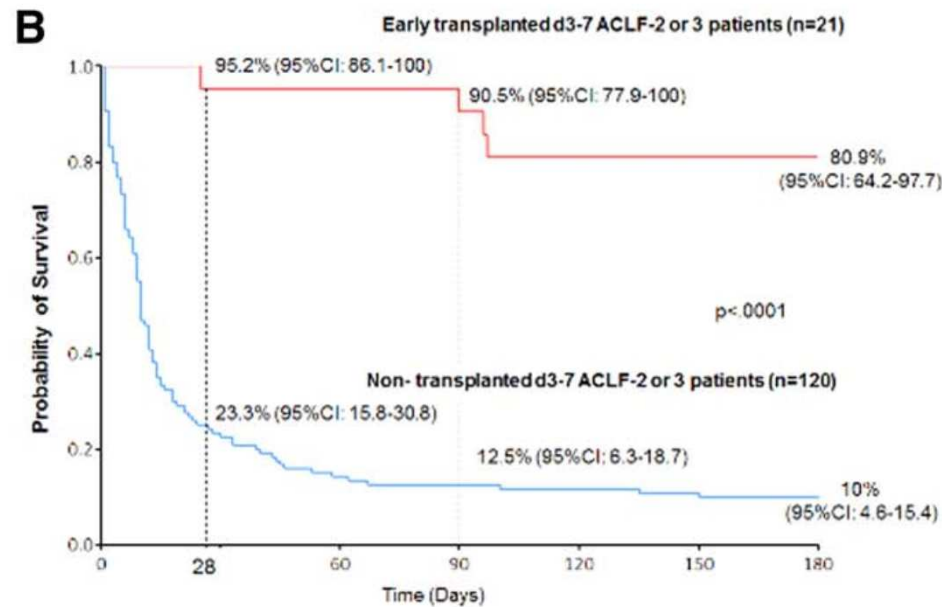
# Bacterial translocation, systemic inflammation and mitochondrial



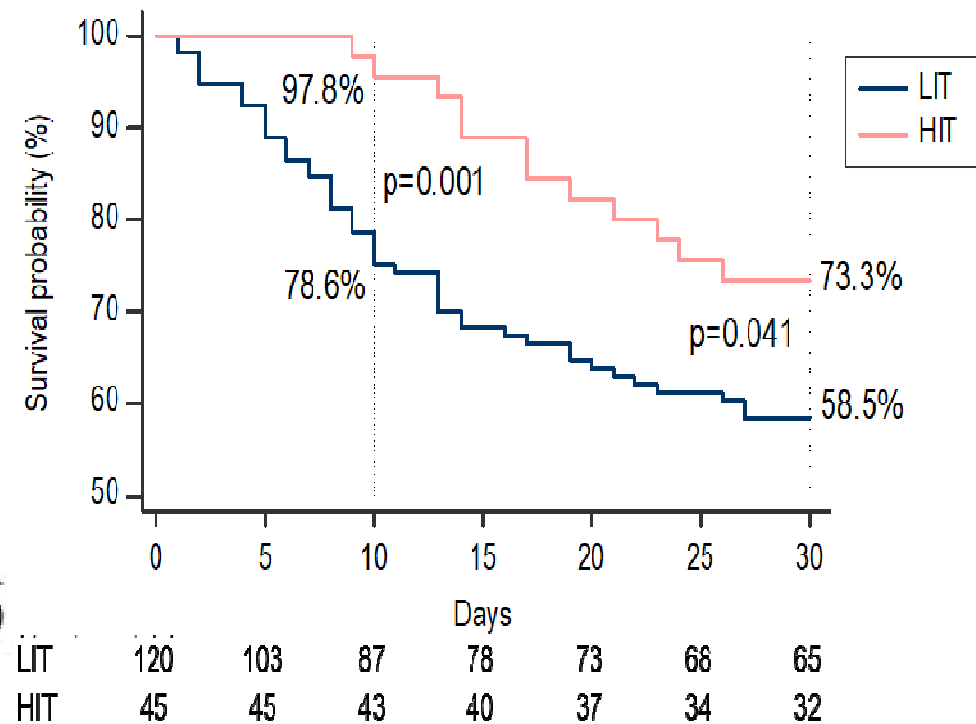
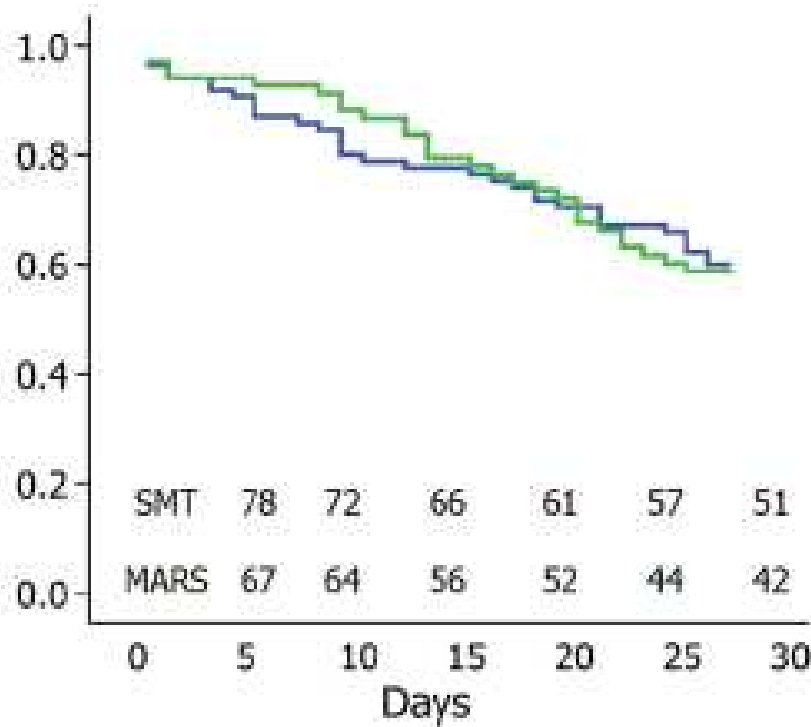
# Management and Prevention



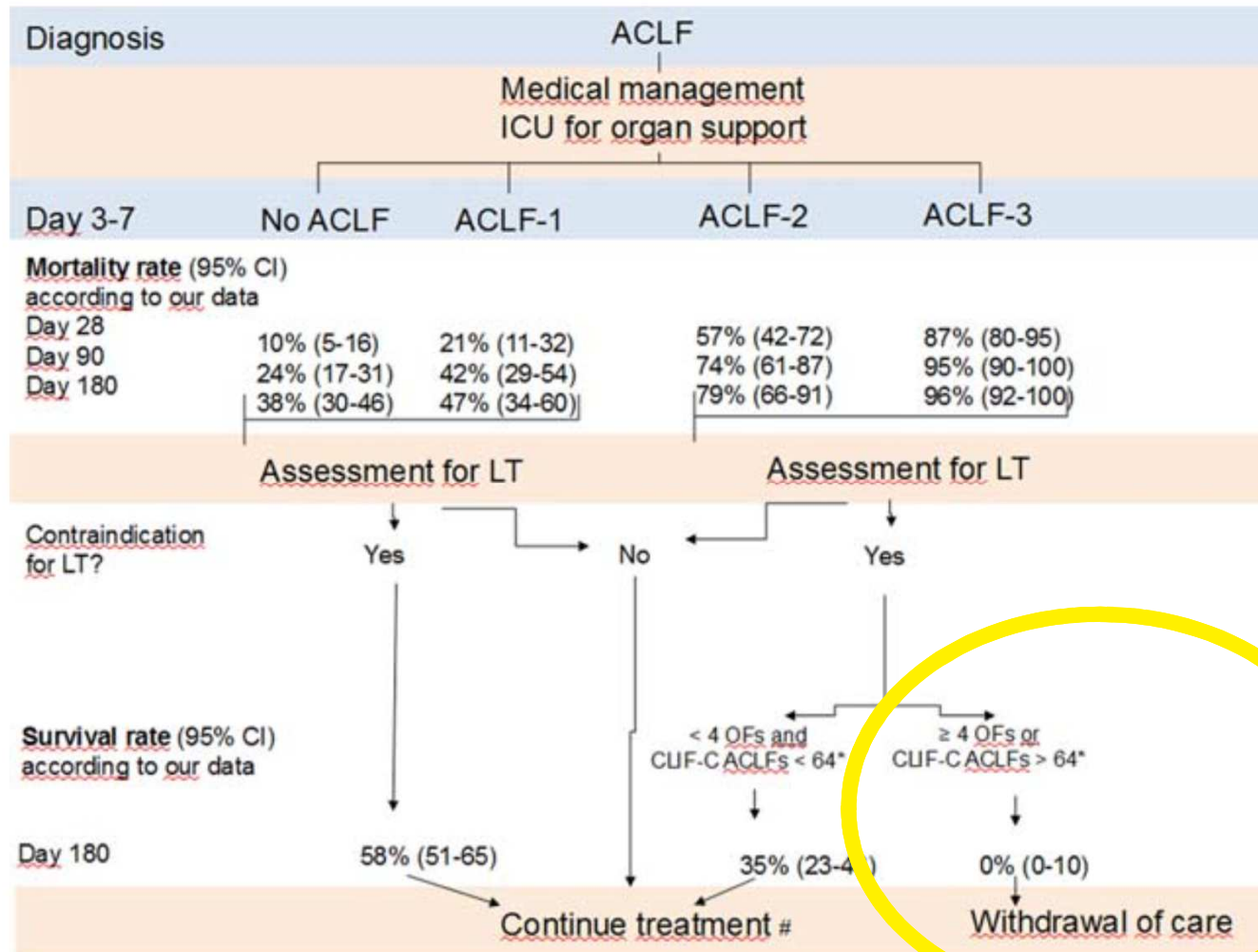
# Liver transplantation is very effective

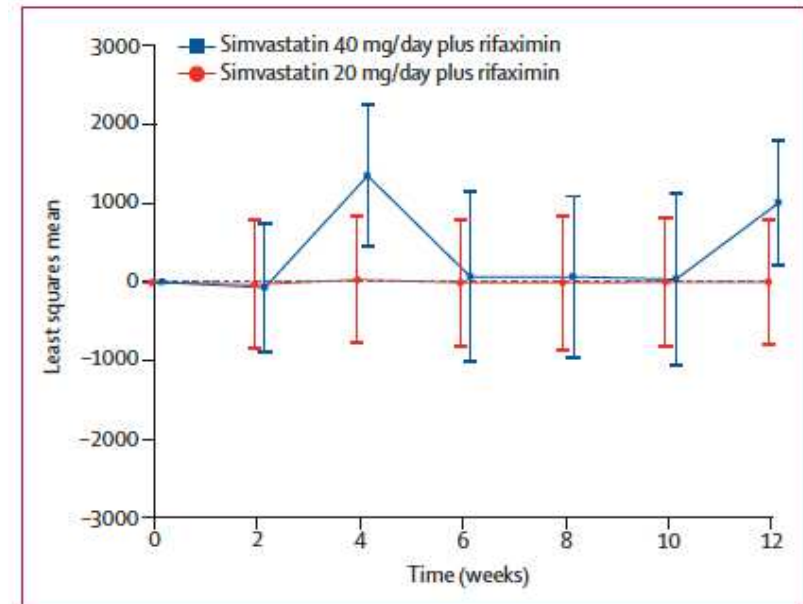
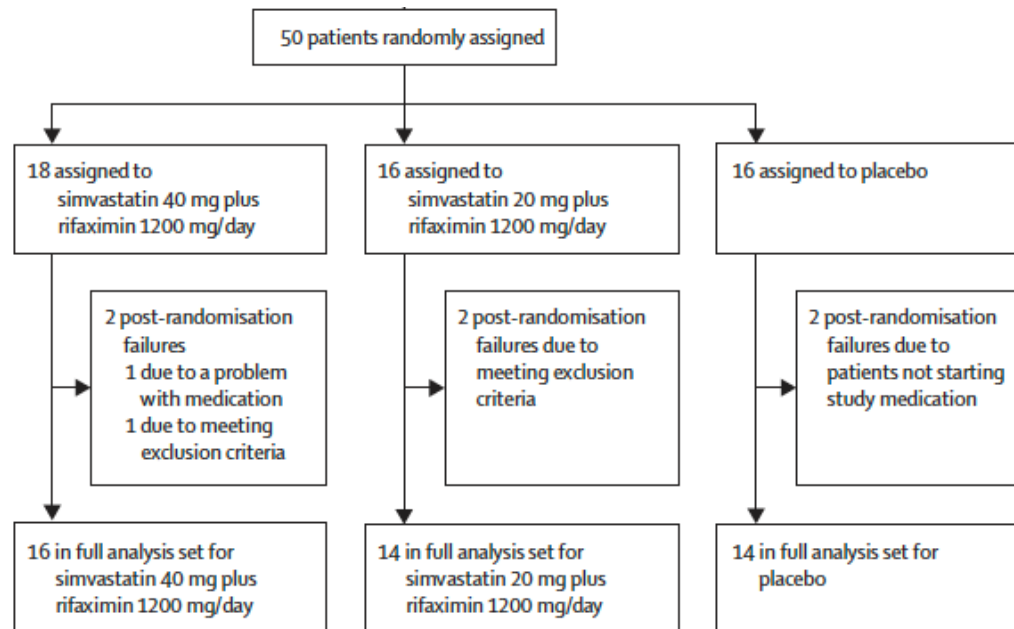


# MARS (albumin dialysis)

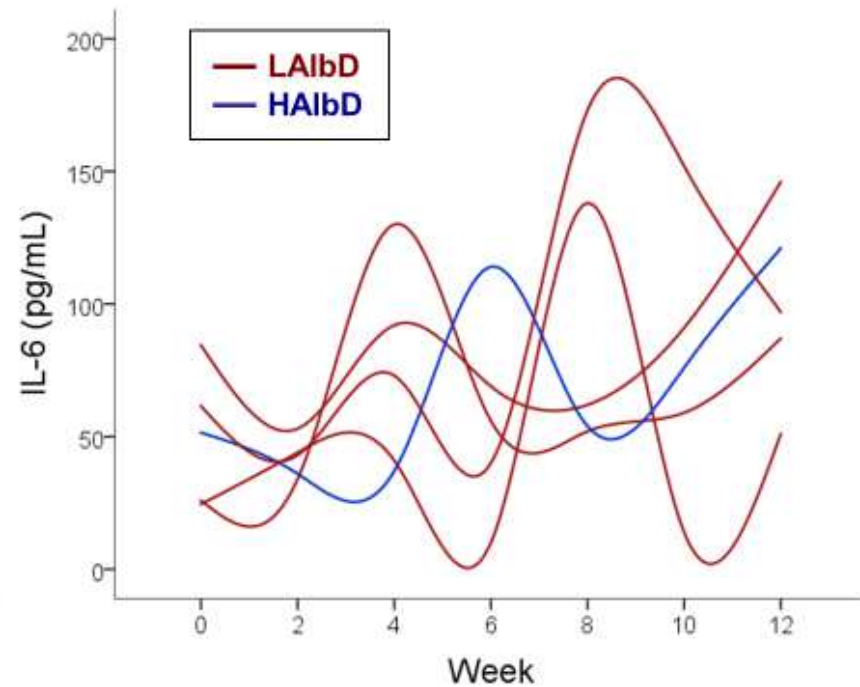
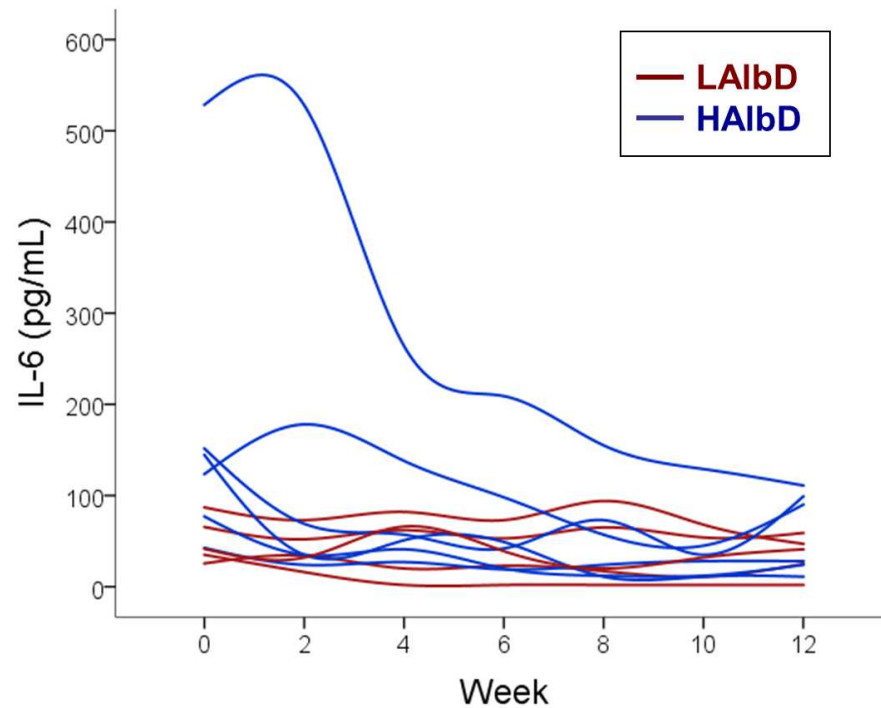


# Futility of care





# ALBUMIN TREATMENT AND SYSTEMIC INFLAMMATION



# Summary



ACLF is a dramatic syndrome with very high mortality and morbidity.

Systemic inflammation and mitochondrial dysfunction characterizes ACLF development.

Probably is the trigger the microbiome either directly deriving from the gut, and/or already in the circulating cells.

Management of ACLF is challenging, liver transplantation as the most promising treatment. Prevention of ACLF would be a better strategy.





# Thank you

