

**EF Clif**

EUROPEAN  
**FOUNDATION**  
FOR THE STUDY  
OF CHRONIC  
LIVER FAILURE



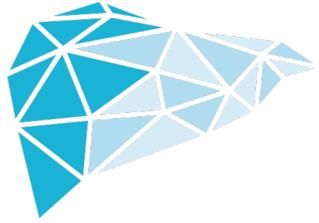
**Royal Free London**  
NHS Foundation Trust



# Advances in ACLF

**Rajiv Jalan**

Professor of Hepatology, UCL; Consultant, Royal Free Hospital  
Scientific Director, EFCLIF



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# Disclosures

**Inventor:** Ornithine Phenylacetate. Licensed by UCL to Mallinckrodt Pharma

**Speaker and Grant Review:** Grifols

**Research Collaboration:** Yaqrit Ltd.

**Founder:** Yaqrit Ltd.; Hepyx Ltd.; Cyberliver Ltd



**UCL**

# Growing worldwide burden of liver disease with few treatment options



**844 MILLION**

people suffering from chronic liver disease in the world<sup>(1)</sup>

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**2 MILLION+**

deaths per year worldwide, a rising number<sup>(1)</sup>

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**TOP 5**

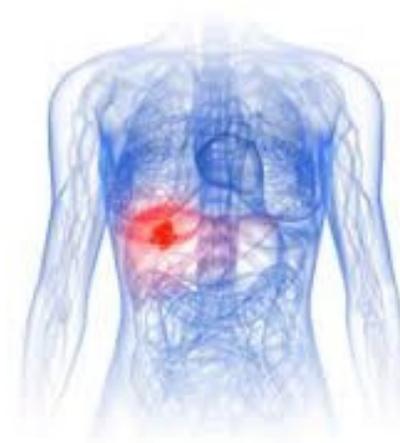
biggest cause of death in the US in middle age<sup>(2)</sup>

**\$18BN+**

US Healthcare Cost<sup>(3)</sup>

**>\$750,000 PER PATIENT**

First 12 month costs of liver transplantation in the US<sup>(4)</sup>



**Few treatment options available**

Two approved drugs target late stage liver diseases:

*Rifaximin* - Gut-acting antibiotic for hepatic encephalopathy

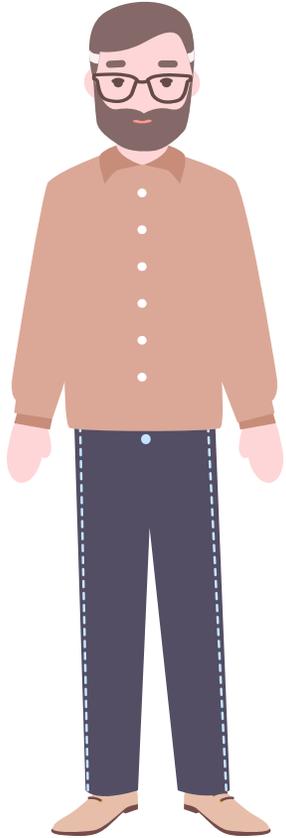
*Ocaliva* - FXR agonist for primary biliary cholangitis

<sup>3</sup> Trends in the Burden of Chronic Liver Disease Among Hospitalized US Adults, JAMA April 2020. <sup>4</sup> Habka D., Mann D., Landes R. and Soto-Gutierrez A. (2015). Future Economics of Liver Transplantation: A 20-Year Cost Modeling Forecast and the Prospect of Bioengineering Autologous Liver Grafts. *PLoS One*.

Source: <sup>1</sup> Ntandja-Wandji, Line-Carolle & al., (2020). Combined alcoholic and non-alcoholic steatohepatitis. *JHEP Reports*. <sup>2</sup> National Vital Statistics Reports, Deaths: Leading Causes for 2017.



# One patient's journey .....



David, a 52-year old accountant, drinking 2 large glasses of wine per day diagnosed with alcoholic cirrhosis on routine health check.

No known liver disease

5 yrs



Admitted to hospital with **pneumonia**. On admission the patient had **fever (38°C)**, **leukocytosis (12.500/ml)**, **high CRP (52 mg/L)**, **ascites, jaundice (bilirubin 5 mg/dl)**.

5 days

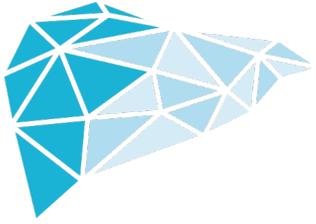


The patient develops hepatic encephalopathy (grade 3) and progressive jaundice (bilirubin: 16 mg/dl) was admitted to the ICU.

He died 5 days later with progressive of liver, renal, circulatory and cerebral failure.

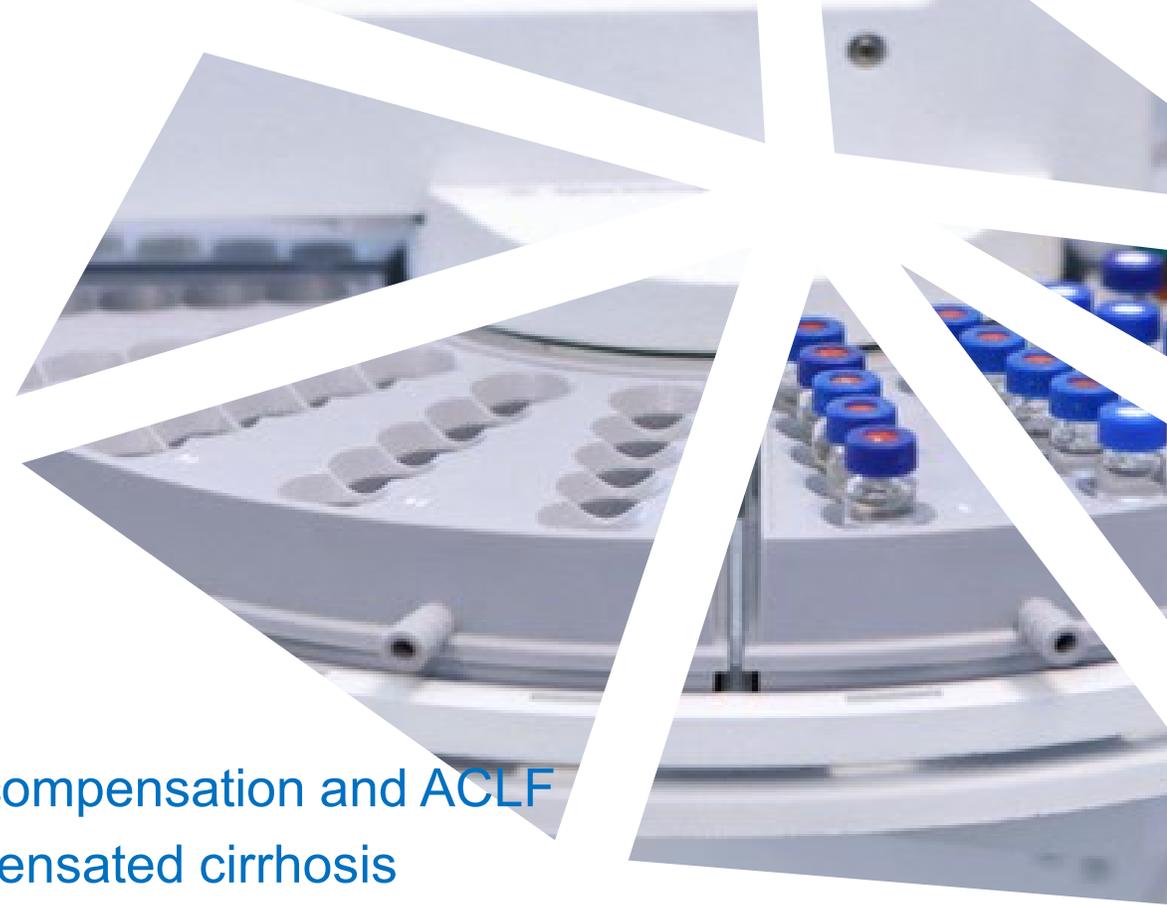
## • The Mystery.....

- What is this syndrome?
- Why does it occur?
- What can be done to reduce the mortality

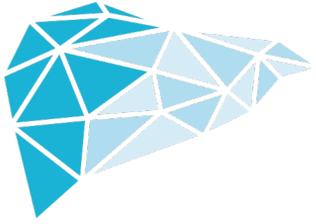


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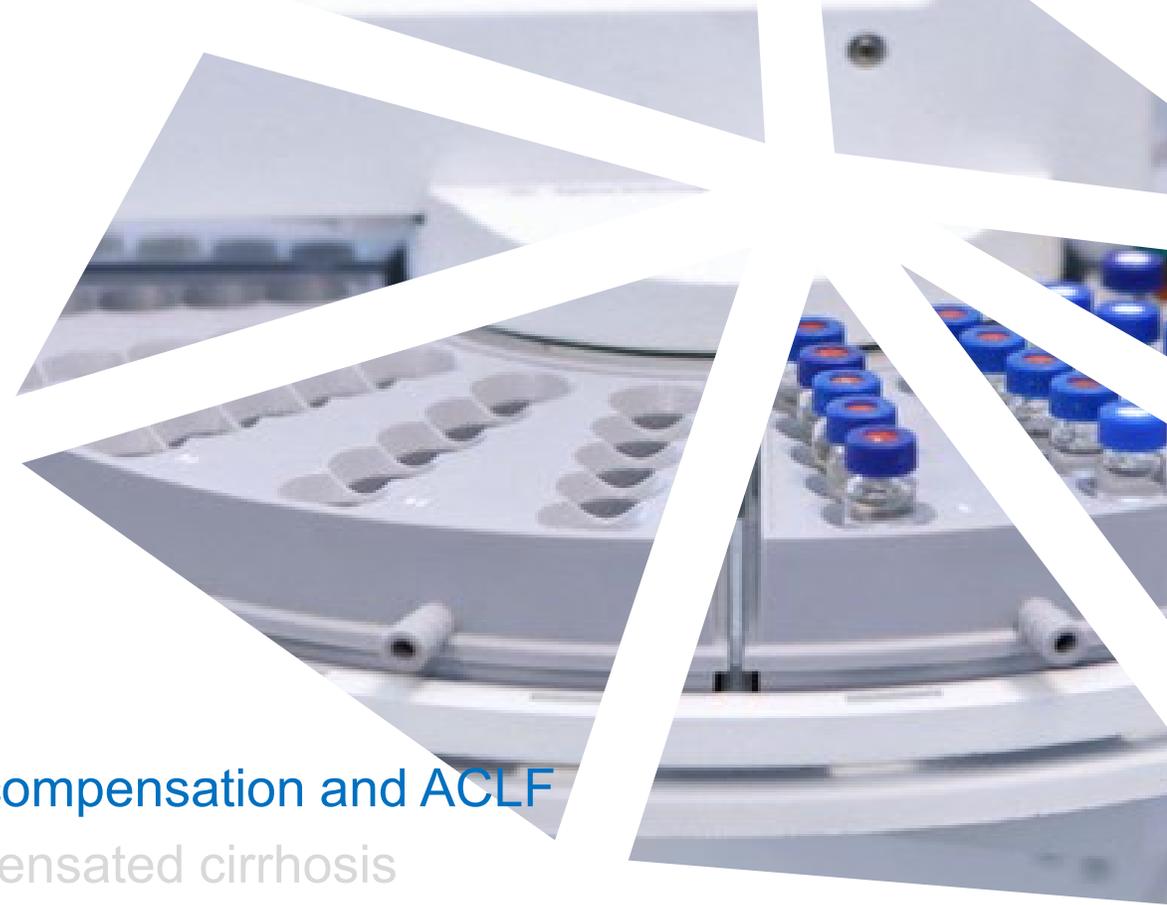


- ACLF and CLIF Consortium: Re-classifying Acute Decompensation and ACLF
- Changing the pathophysiological paradigm of decompensated cirrhosis
- Developing new therapies in the ACLF space
- 1<sup>st</sup> smell of therapeutic success: Liver Transplantation – The CHANCE study
- Prevention of ACLF and its recurrence



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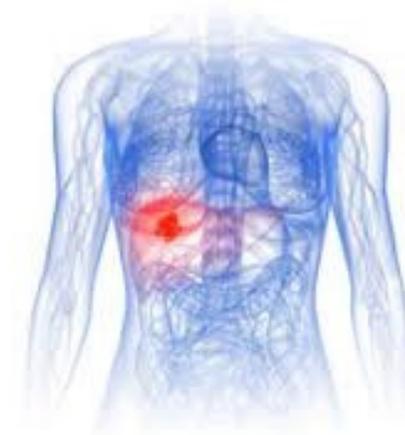
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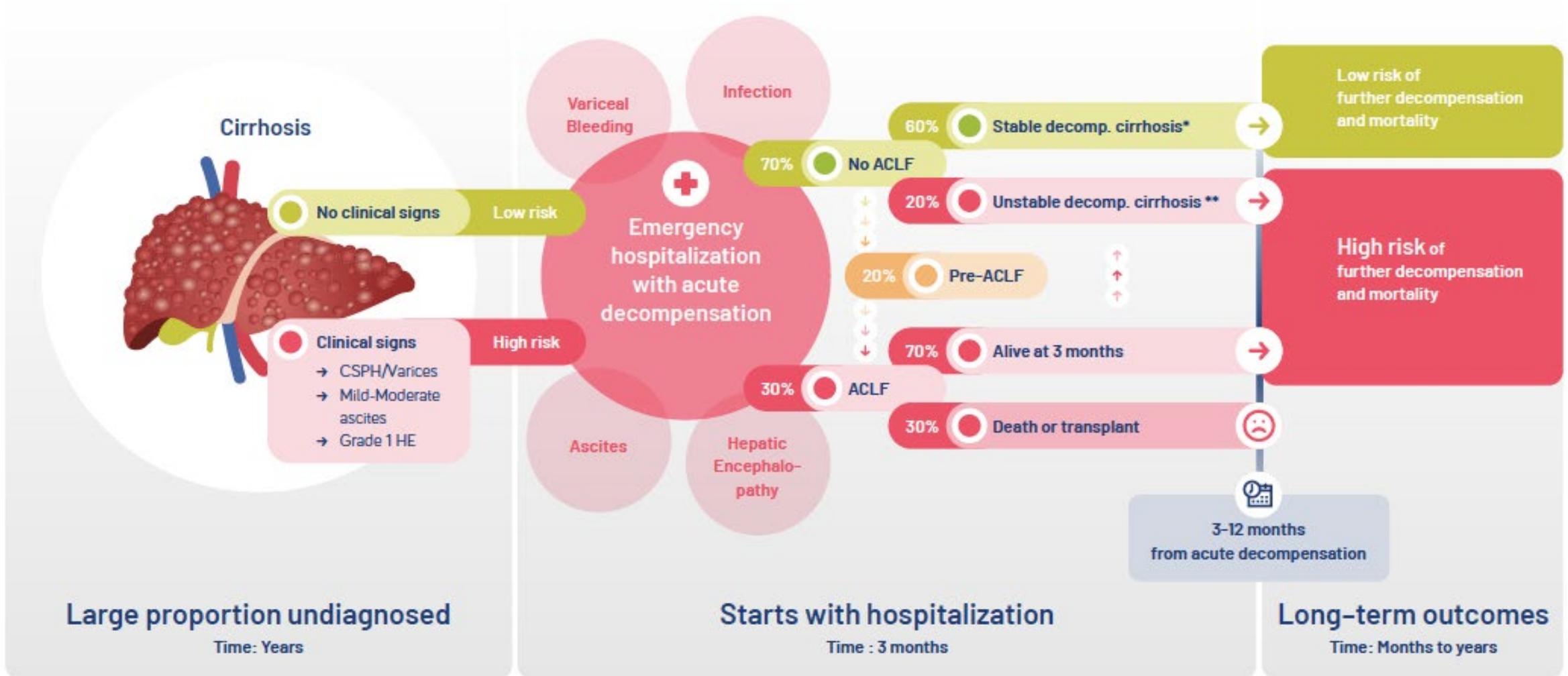
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# Trajectory of Cirrhosis



\* Stable Decomp Cirrhosis: 100% Survival over 3-months \*\* Unstable Decomp Cirrhosis: 70% Survival over 3-months \*\*\* pre ACLF: 50% Survival over 3-months  
CSPH: Clinically significant portal hypertension

# What do we have at present?

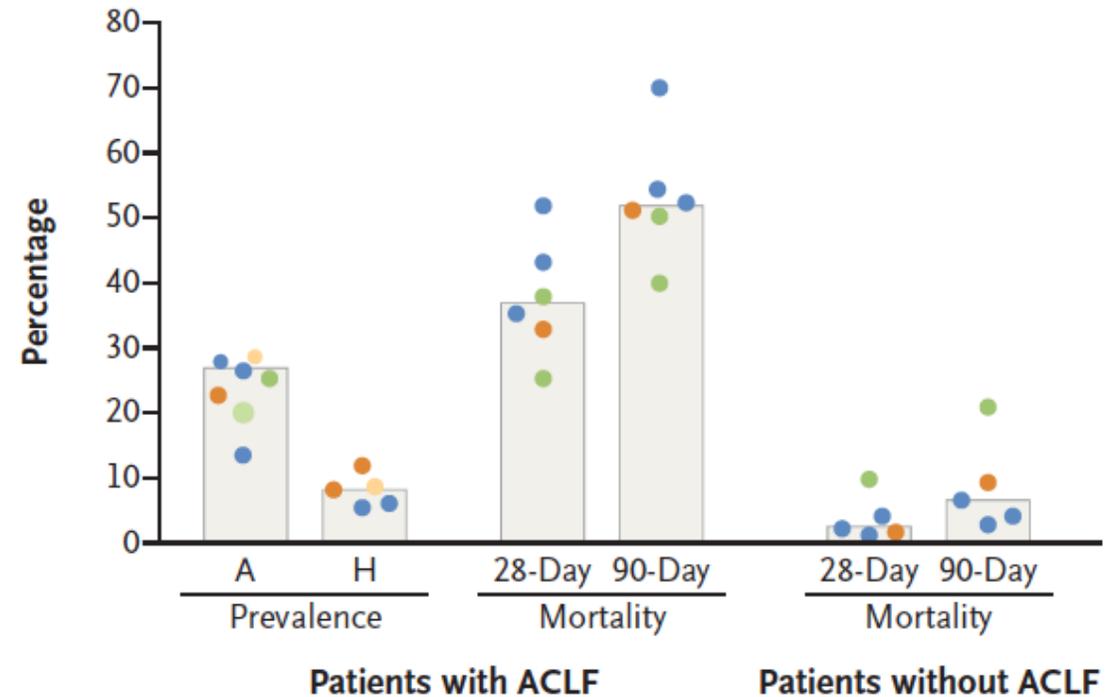
## Diagnostic criteria of organ dysfunction and failure

Organ System	1 point	2 points	3 points
Liver	Bilirubin < 6 mg/dL	Bilirubin 6-11.9 mg/dL	Bilirubin ≥ 12 mg/dL
Kidney	Creatinine < 1.5 mg/dL	Creatinine 2-3.4 mg/dL	Creatinine ≥ 3.5 mg/dL or RRT
	Creatinine 1.5-1.9 mg/dL		
Brain (West Haven Score)	Grade 0	Grade 1-2	Grade 3-4
Coagulation	INR < 2.0	INR 2.0-2.4	INR ≥ 2.5
Circulation	MAP ≥ 70 mmHg	MAP < 70 mmHg	Vasopressor requirement
Respiratory	PaO <sub>2</sub> /FiO <sub>2</sub> > 300	PaO <sub>2</sub> /FiO <sub>2</sub> 201-300 SpO <sub>2</sub> /FiO <sub>2</sub> 215-357	PaO <sub>2</sub> /FiO <sub>2</sub> ≤ 200 SpO <sub>2</sub> /FiO <sub>2</sub> ≤ 214
	SpO <sub>2</sub> /FiO <sub>2</sub> > 357		

## Diagnostic criteria of ACLF and ACLF grades

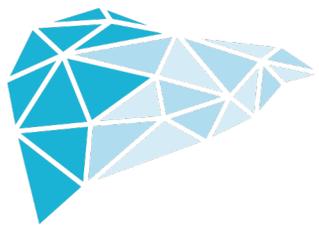
Patients group	Prevalence over 1287 patients (%)	28-day Mortality (%)	Assigned category
Absence of OF	68.3	4.4	Absence of ACLF
Single non Kidney OF without KD or BD	9.9	6.3	
Single KF	6.7	18.6	ACLF-1
Single non Kidney OF with KD or BD	4.2	27.8	ACLF-1
Two OFs	7.5	32.0	ACLF-2
Three OFs	1.9	68.0	ACLF-3
Four to six OFs	1.4	88.9	ACLF-3

Arroyo, Moreau Jalan NEJM 2020

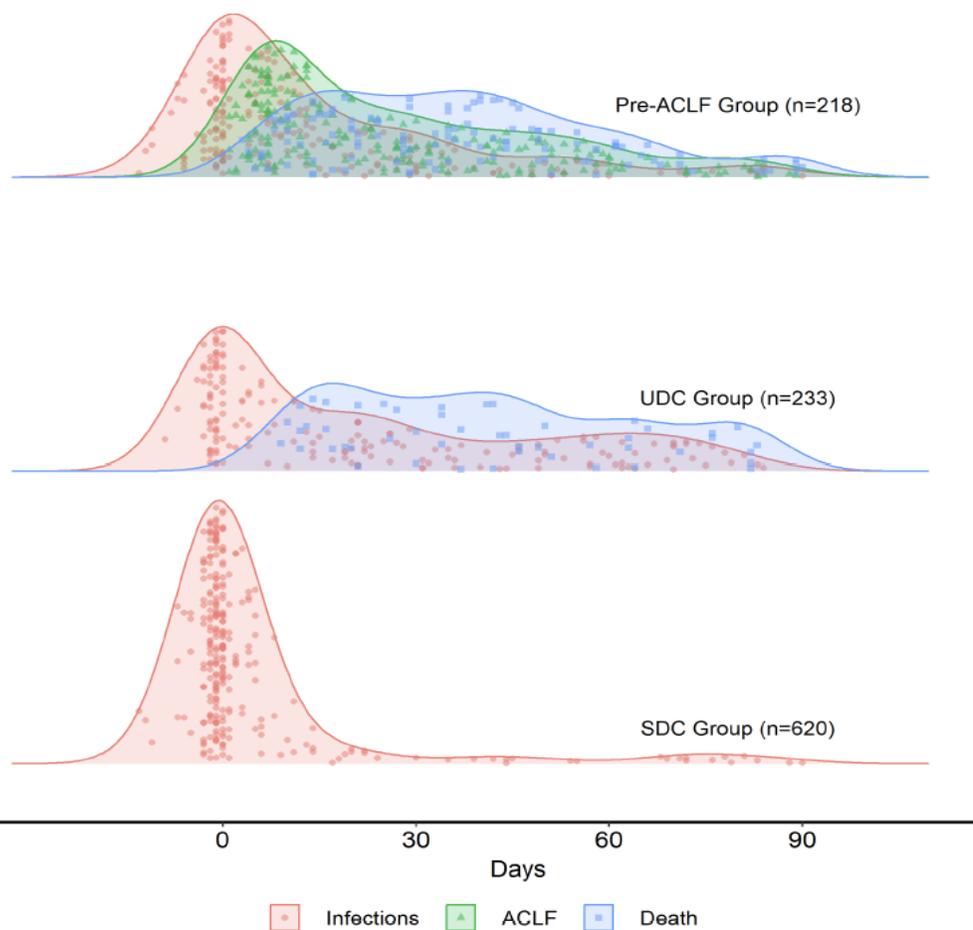


- **Europe: CANONIC and PREDICT (n=1343; n=1375);**
- **Asia: Li et al. (n=890), KACLIF (n=1235 patients), COSSH (n=1031)**
- **USA: Mahmud et al. (n=80,383 patients) and Hernaez et al. (n=72,316)**
- **Latin America: ACLARA (n=1077)**

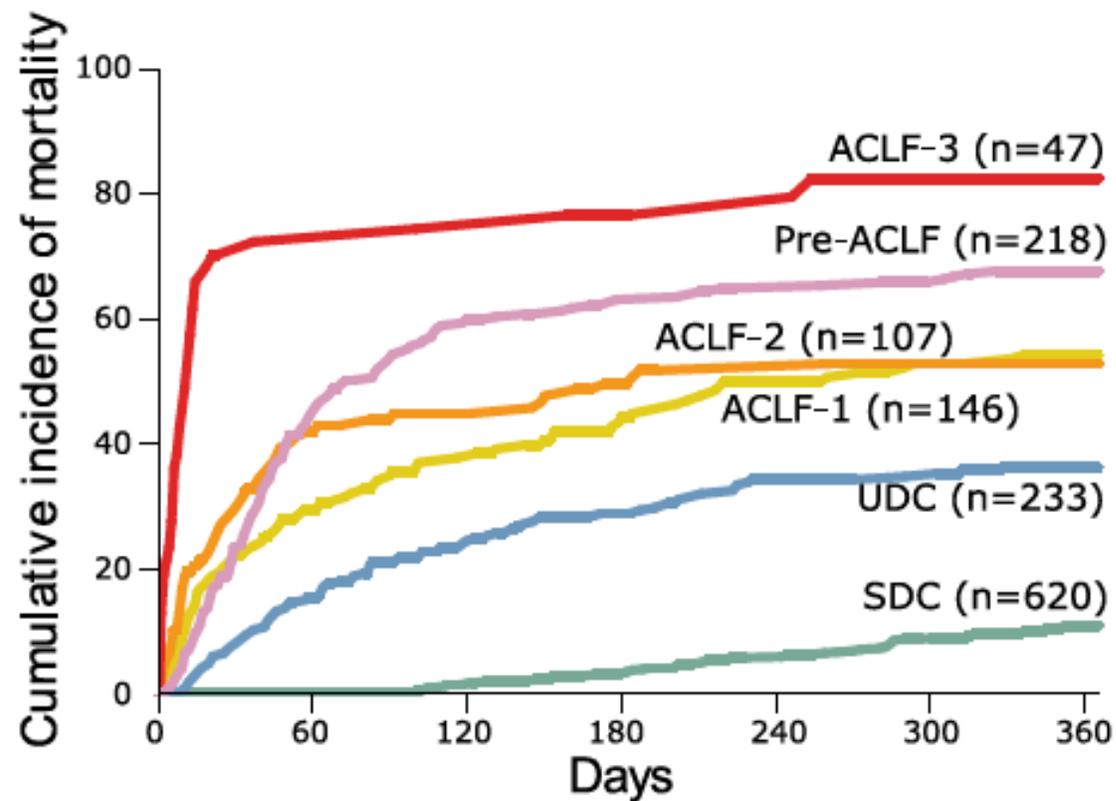
# Reclassifying decompensated cirrhosis



## 3-phenotypes of Acute decompensation, No ACLF

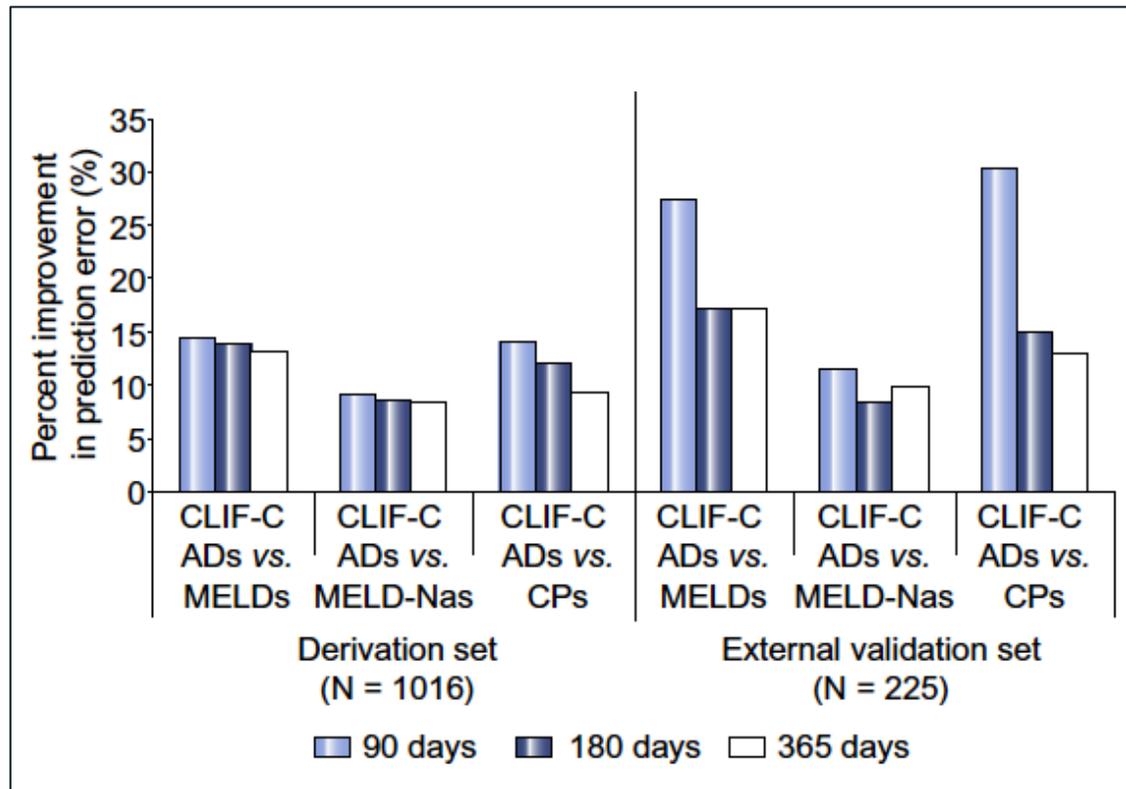


## Overall decompensation: 6-clinical phenotypes of patients with acute

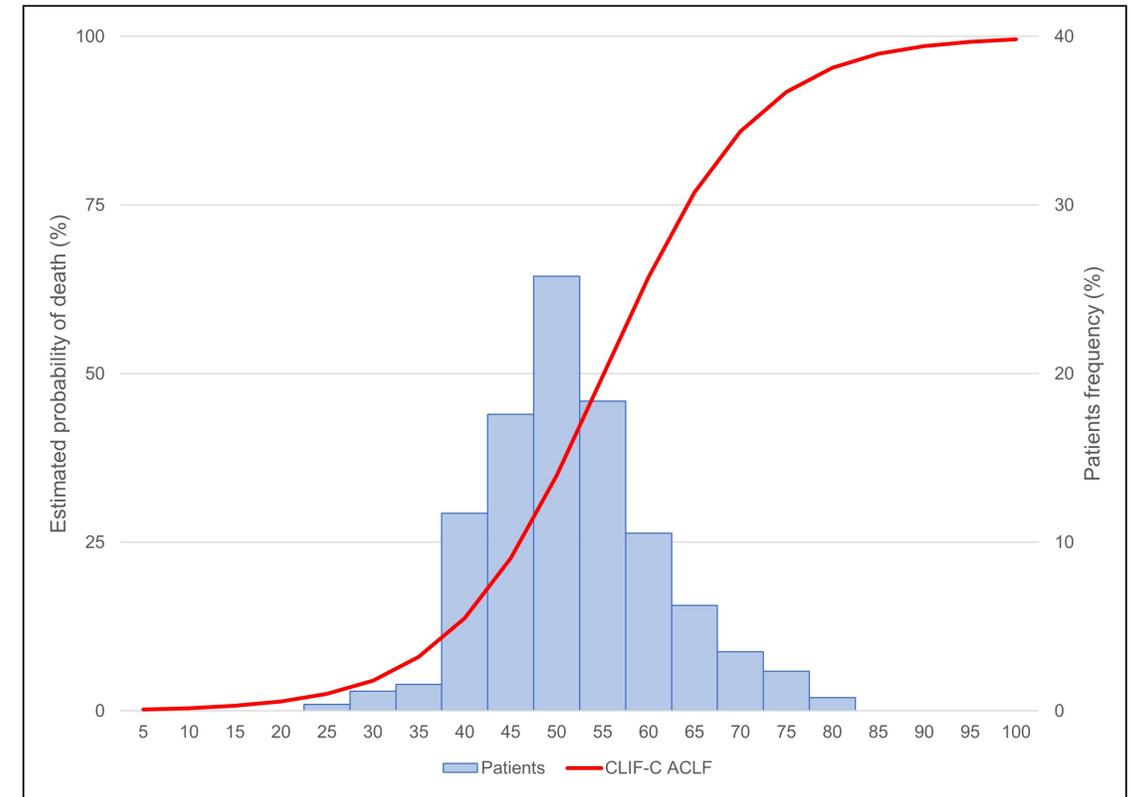


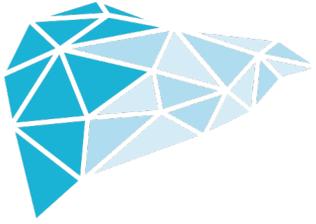
# Prognostic Models: The CLIF-C ADs and the CLIF-C ACLFs perform better than other prognostic models

CLIF-C ADs: AUC - 0.72



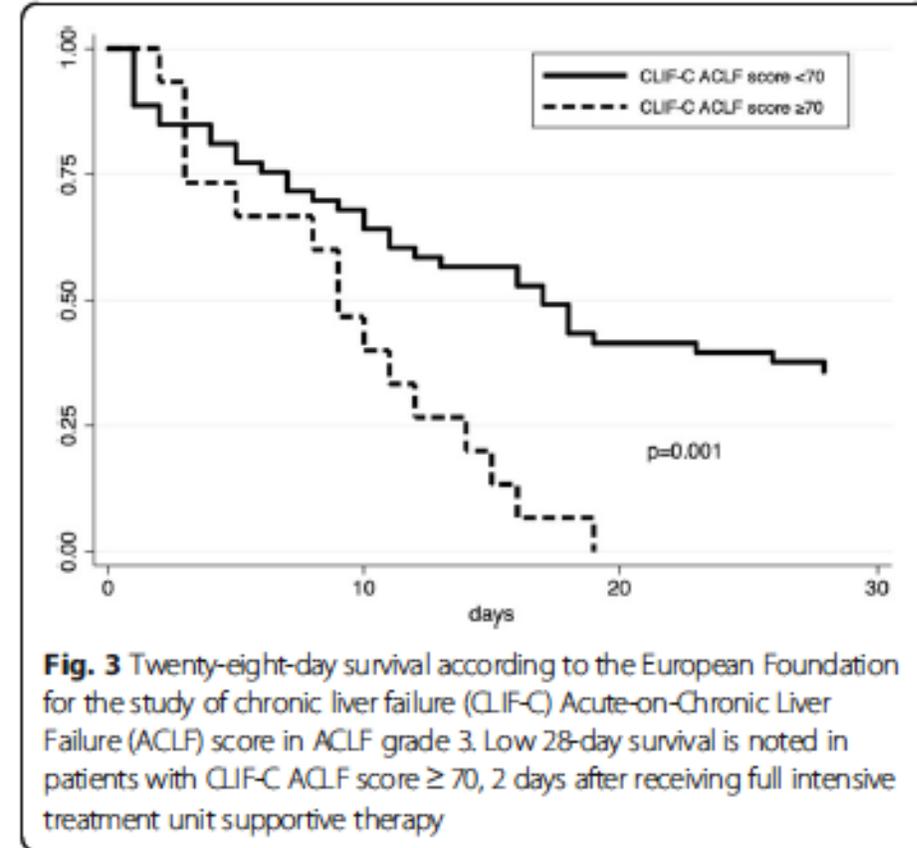
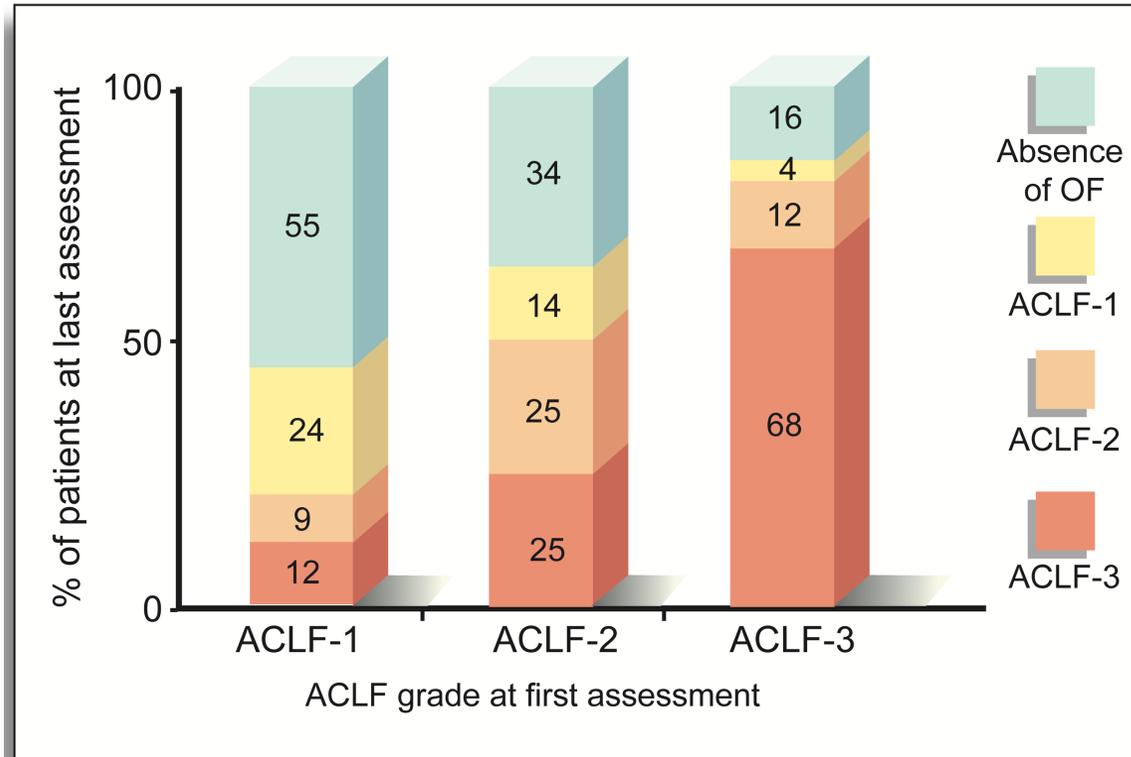
CLIF-C ACLF s: AUC - 0.74

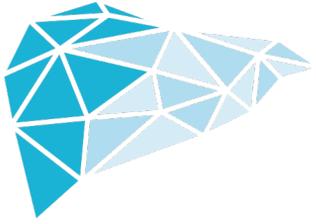




# Potential reversibility and Futility

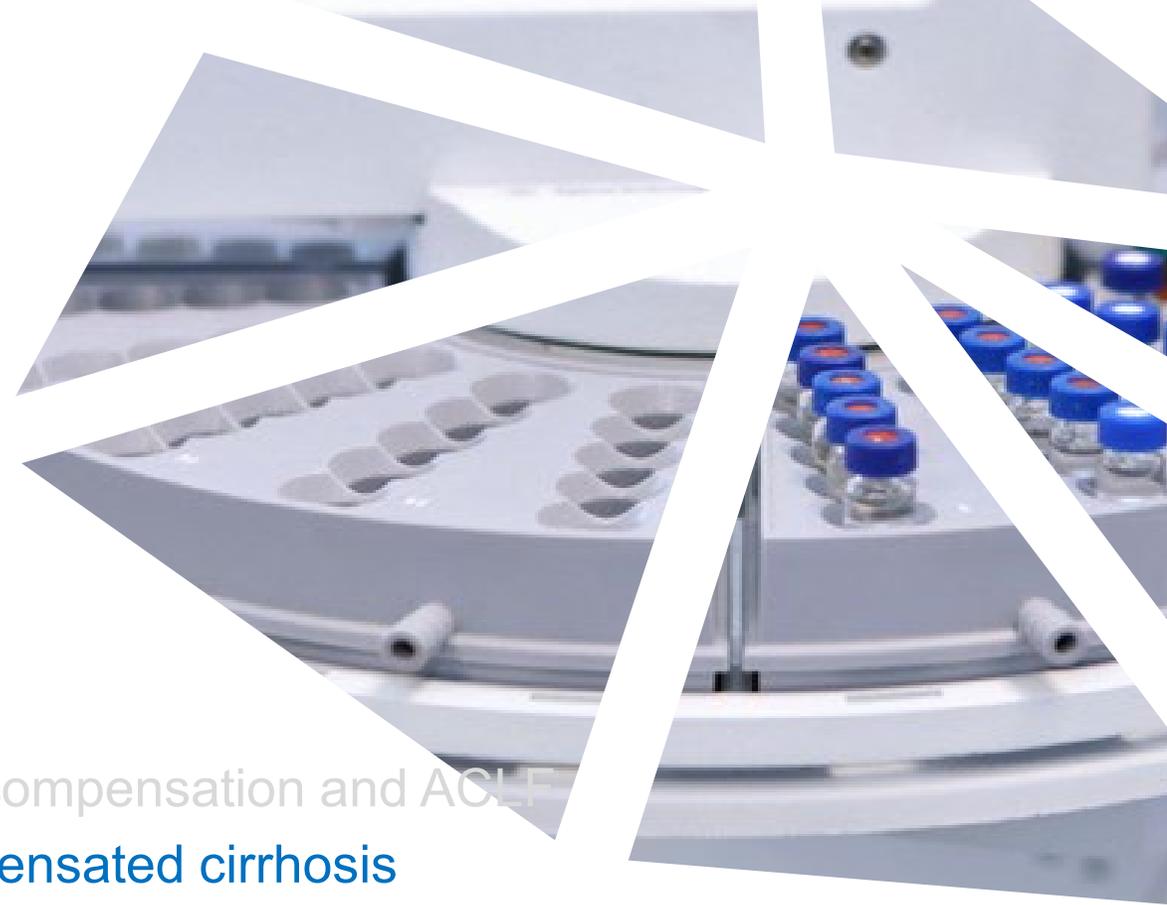
## Clinical course of ACLF





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# Pathophysiology of decompensated cirrhosis: a progressive unveiling...

1988

0270-9139/88/0805-1151\$02.00/0

HEPATOLOGY

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Vol. 8, No. 5, pp. 1151-1157, 1988

*Printed in U.S.A.*

## Special Article

### Peripheral Arterial Vasodilation Hypothesis: A Proposal for the Initiation of Renal Sodium and Water Retention in Cirrhosis

ROBERT W. SCHRIER, VICENTE ARROYO, MAURO BERNARDI, MURRAY EPSTEIN, JENS H. HENRIKSEN AND  
JOAN RODÉS

1988  2007  2015

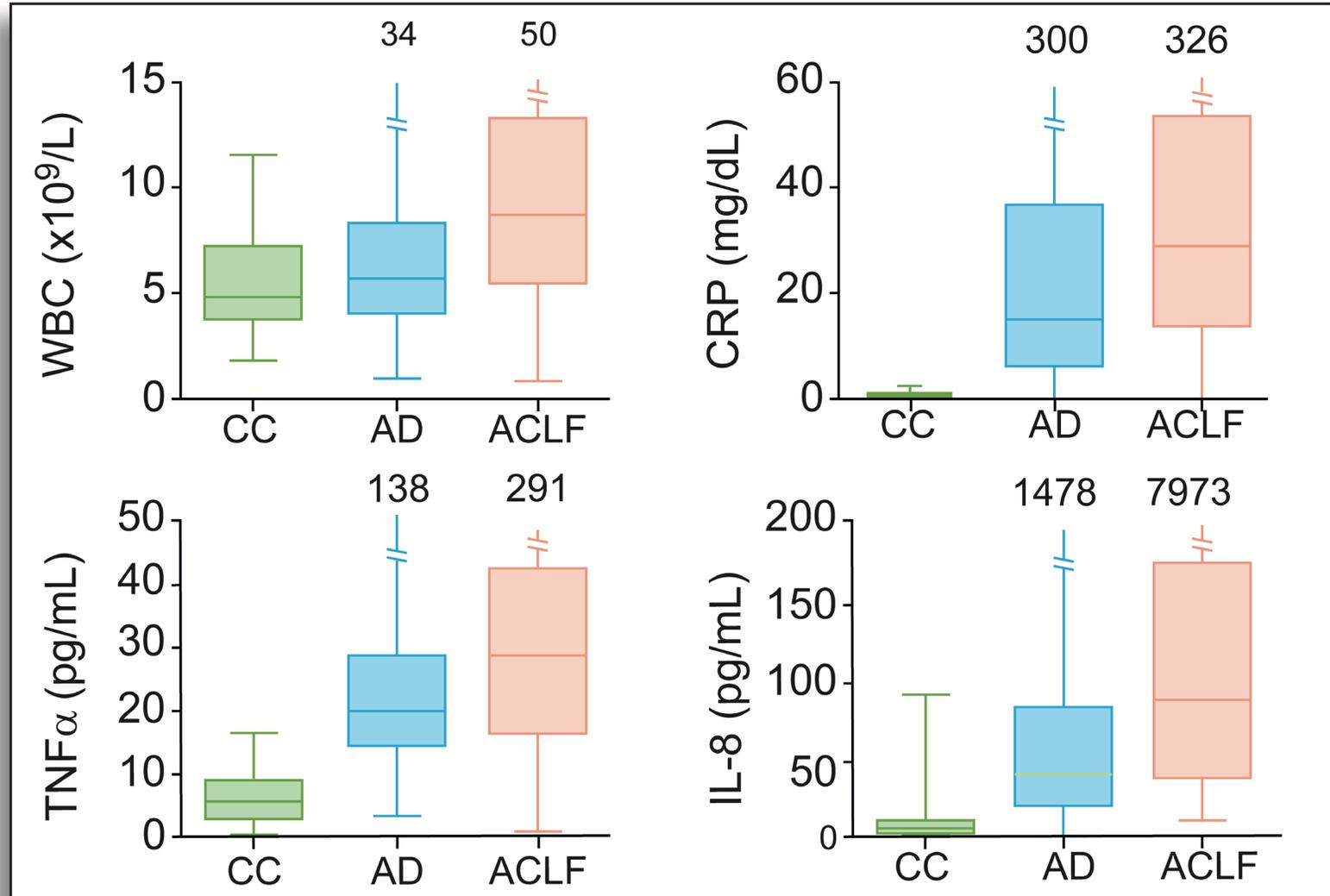
Hypothesis



**Mechanisms of decompensation and organ failure in cirrhosis:  
From peripheral arterial vasodilation to systemic  
inflammation hypothesis**

Mauro Bernardi<sup>1,2,\*†</sup>, Richard Moreau<sup>3,4,5,†</sup>, Paolo Angeli<sup>6,†</sup>, Bernd Schnabl<sup>7,8,†</sup>,  
Vicente Arroyo<sup>9,10,11,†</sup>

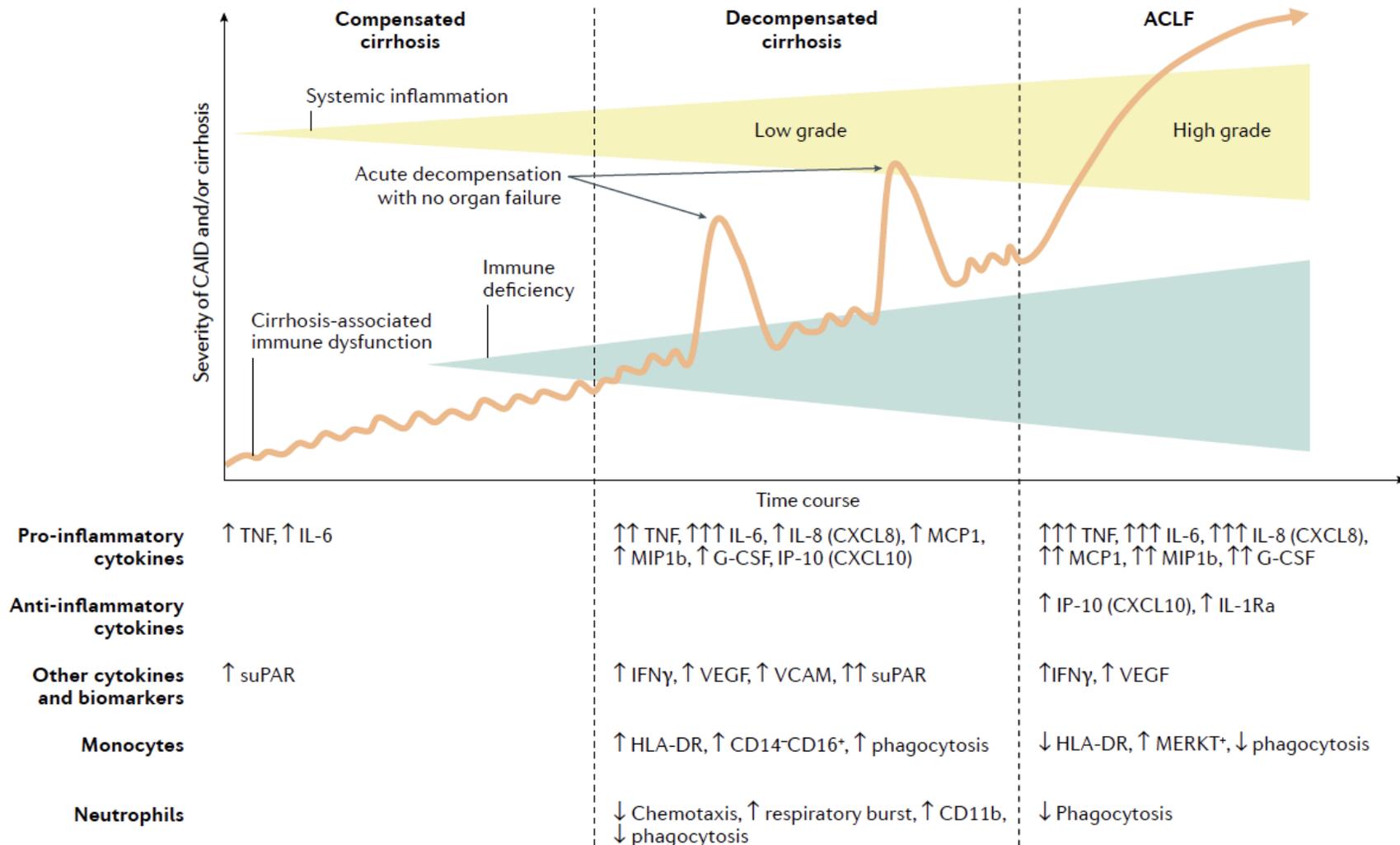
## Inflammatory markers



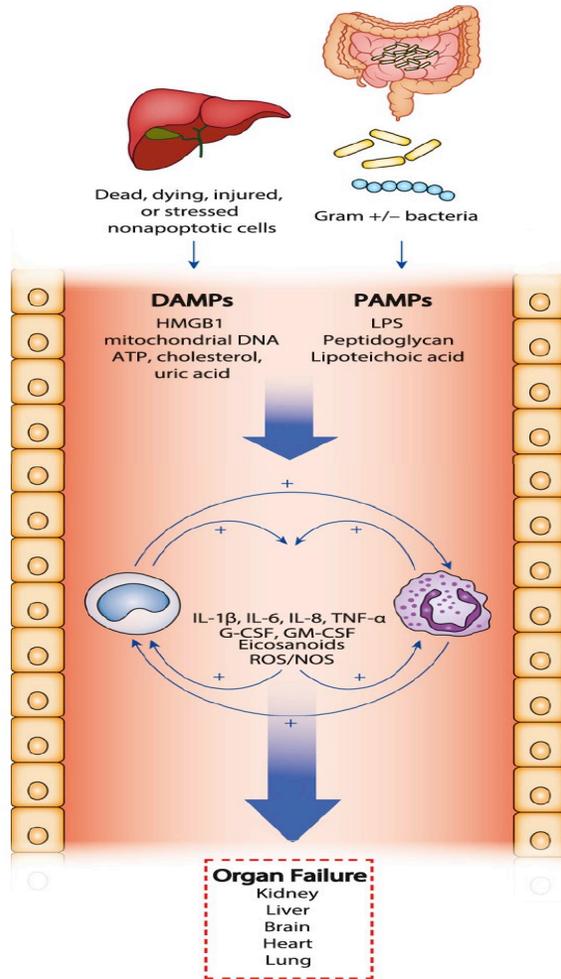
# Cirrhosis-associated immune dysfunction

Agustín Albillos<sup>1,2,3</sup>, Rosa Martín-Mateos<sup>1,2,3</sup>, Schalk Van der Merwe<sup>4,5</sup>,  
Reiner Wiest<sup>6</sup>, Rajiv Jalan<sup>7</sup> and Melchor Álvarez-Mon<sup>2,3,8</sup>

Nature Reviews Gastro Hep. 2021



1988 2007 2015



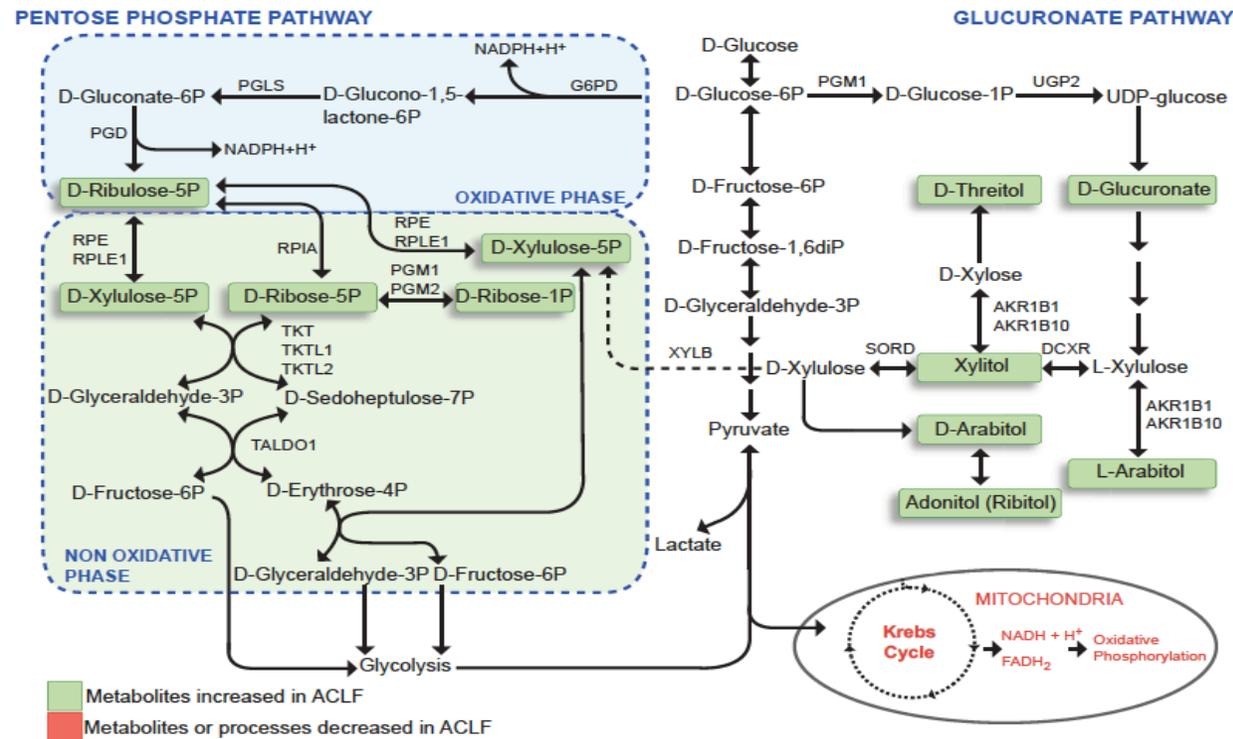
**How systemic inflammation causes organ failure?**

## Immunopathology

- Tissue and cell damage directly produced by immune cells
- ROS and NOS-related injury
- Microcirculatory disturbances
- .....



## Intracellular glucose metabolism switch from mitochondria to cytosol (in immune cells)

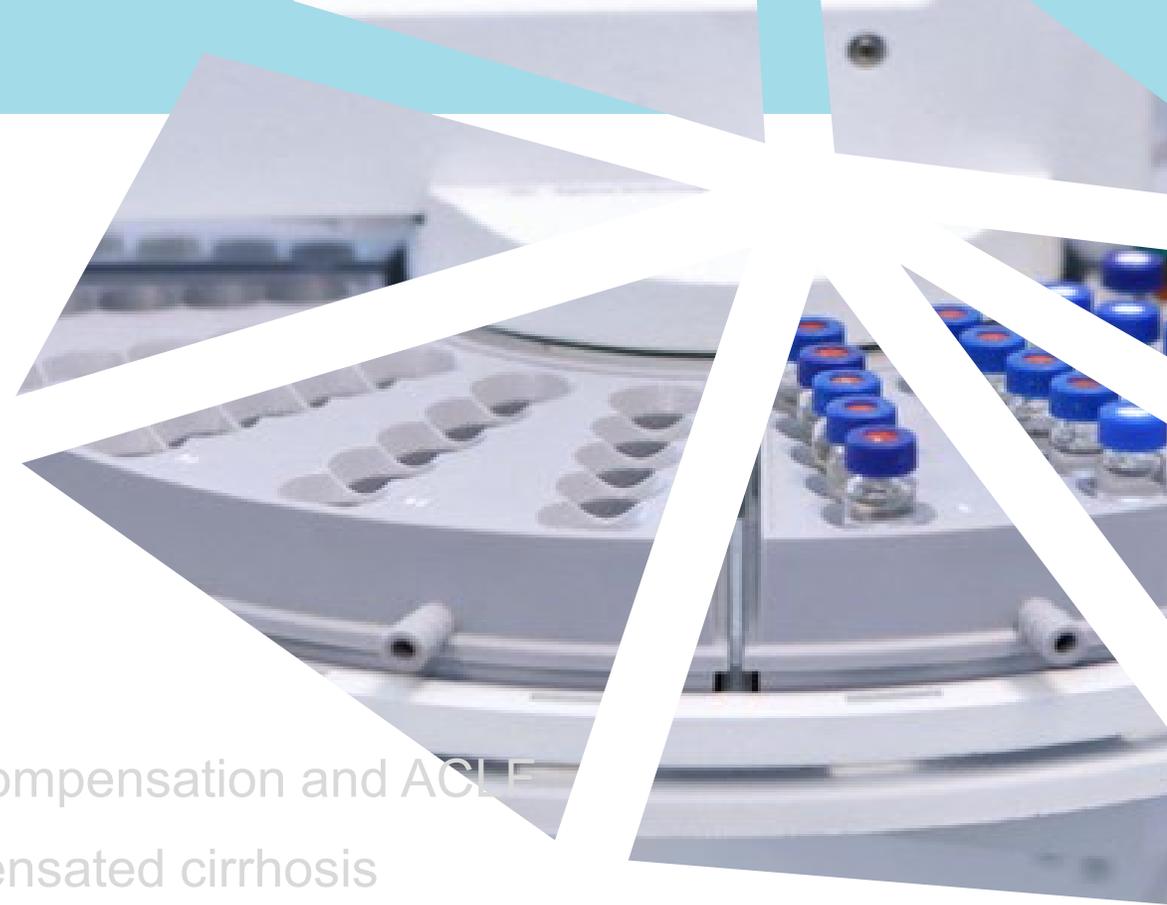


### Systemic inflammation inhibits OxPhos by:

- Reduced conversion of pyruvate to acetyl-CoA entering Krebs' cycle
- Microcirculatory dysfunction, producing mitochondrial ischemic damage
- iNOS up-regulation inducing NO-mediated nitrosylation of electron transport proteins
- .....

### Homeostatic response since:

- Cytosolic glycolysis is energetically less effective in terms of glucose utilization, but more rapid producing more ATP per unit of time
- The pentose phosphate pathways provides biosynthetic molecules that are essential to support immune responses
- .....



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# For drug development in ACLF, standard of care needs to be defined

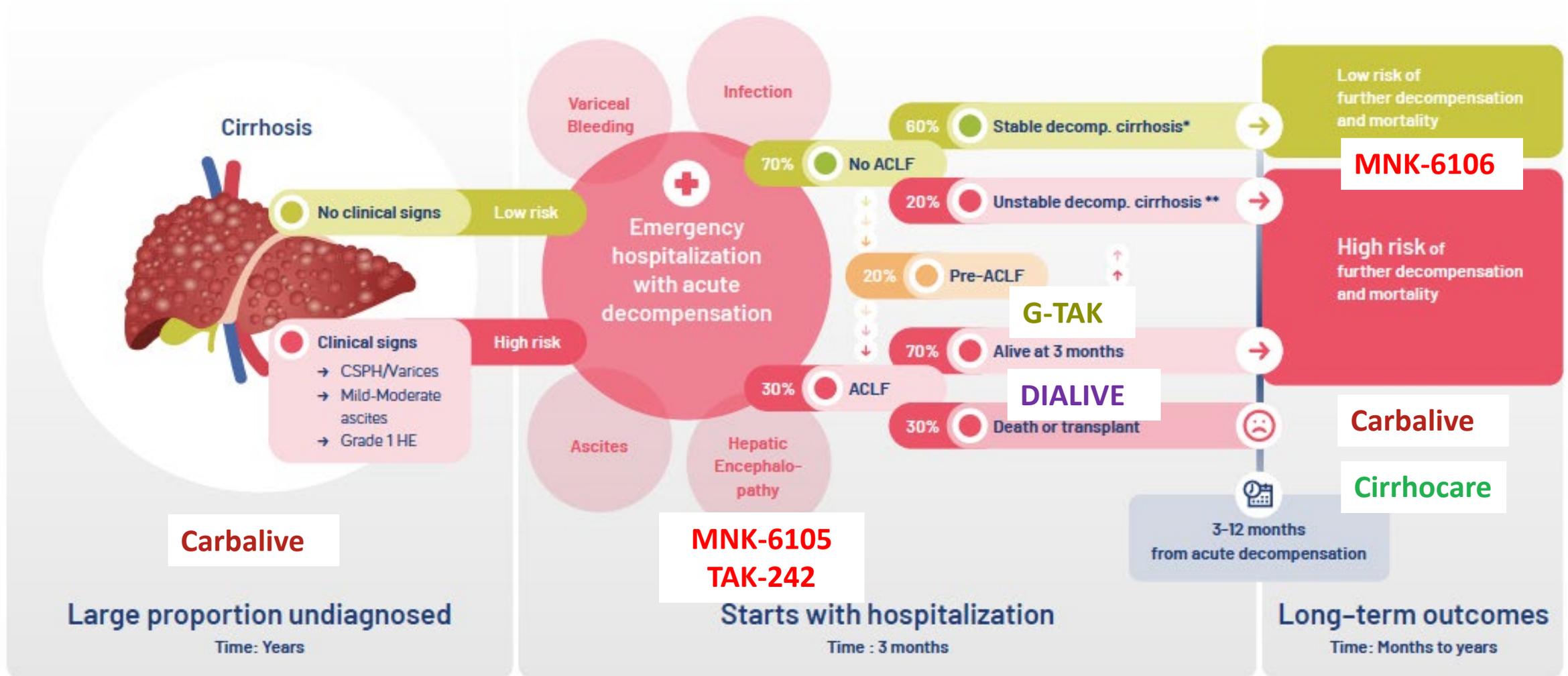
## Defining Standard of Care

- **Definitions**
  - Bleeding, Renal dysfunction, ACLF, Infection,
- **ICU admission criteria**
  - Organ Failures
- **Management of complications**
  - Variceal bleeding, Infection, Encephalopathy, Ascites, Albumin
- **Monitoring**
  - Line placement, Blood Tests
- **Organ Support**
  - Mechanical Ventilation, Renal Replacement, Vasopressor, Plasma Exchange

### Management of the critically ill patient with cirrhosis: A multidisciplinary perspective

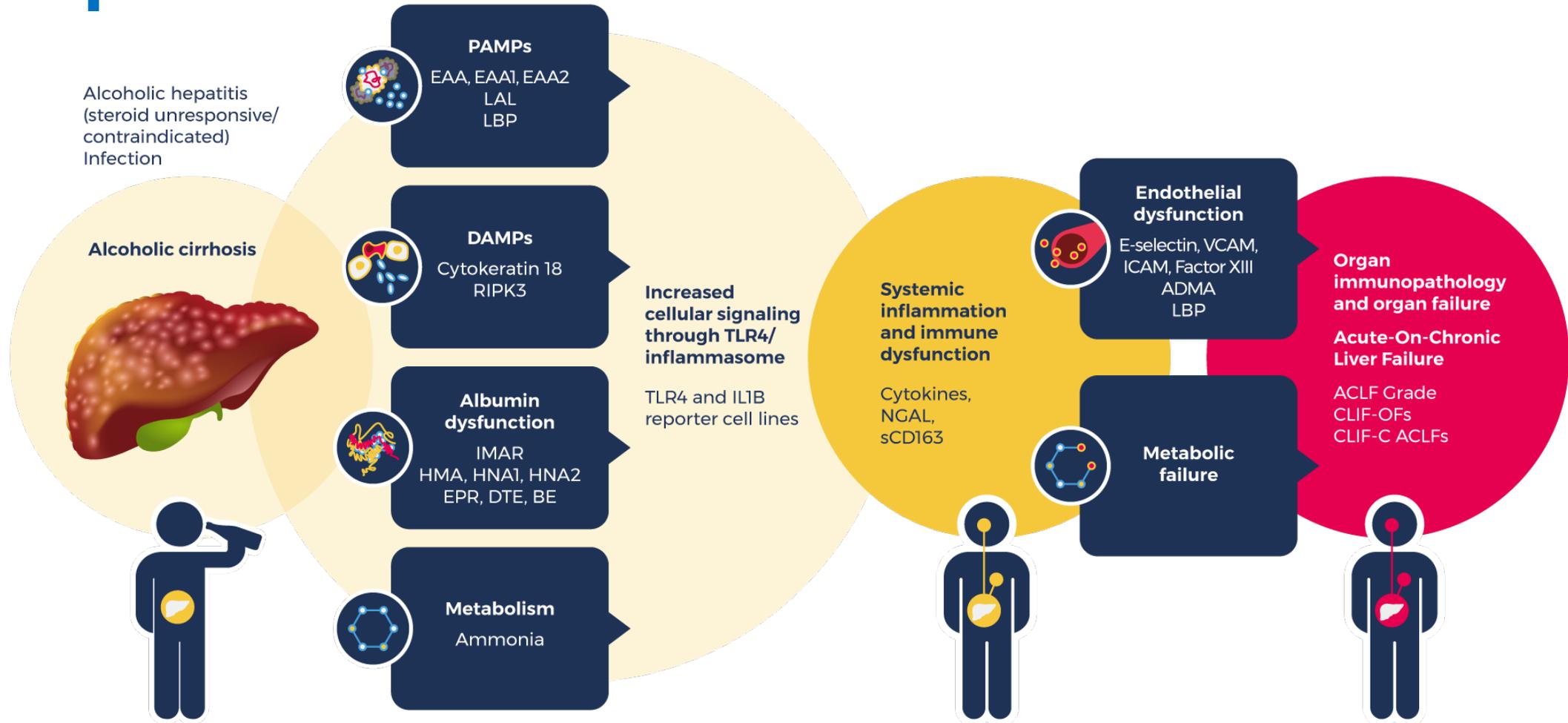
Mitra K. Nadim<sup>1,\*</sup>, François Durand<sup>2</sup>, John A. Kellum<sup>3</sup>, Josh Levitsky<sup>4</sup>, Jacqueline G. O'Leary<sup>5</sup>,  
Constantine J. Karvellas<sup>6</sup>, Jasmohan S. Bajaj<sup>7</sup>, Andrew Davenport<sup>8</sup>, Rajiv Jalan<sup>9</sup>, Paolo Angeli<sup>10</sup>,  
Stephen H. Caldwell<sup>11</sup>, Javier Fernández<sup>12</sup>, Claire Francoz<sup>2</sup>, Guadalupe García-Tsao<sup>13</sup>, Pere Ginès<sup>12</sup>,  
Michael G. Ison<sup>14</sup>, David J. Kramer<sup>15</sup>, Ravindra L. Mehta<sup>16</sup>, Richard Moreau<sup>2</sup>, David Mulligan<sup>17</sup>,  
Jody C. Olson<sup>18</sup>, Elizabeth A. Pomfret<sup>19</sup>, Marco Senzolo<sup>20</sup>, Randolph H. Steadman<sup>21</sup>,  
Ram M. Subramanian<sup>22</sup>, Jean-Louis Vincent<sup>23</sup>, Yuri S. Genyk<sup>24</sup>

# Novel therapies under development

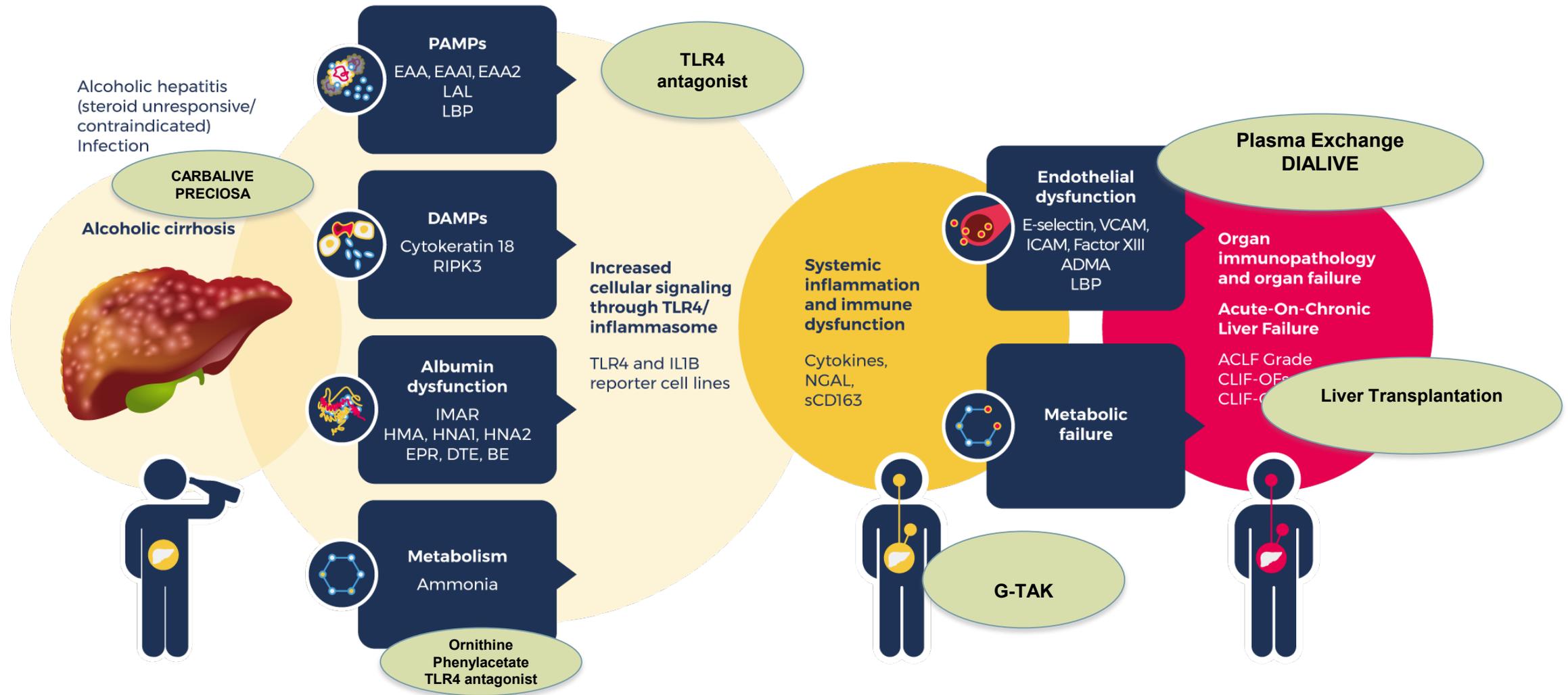


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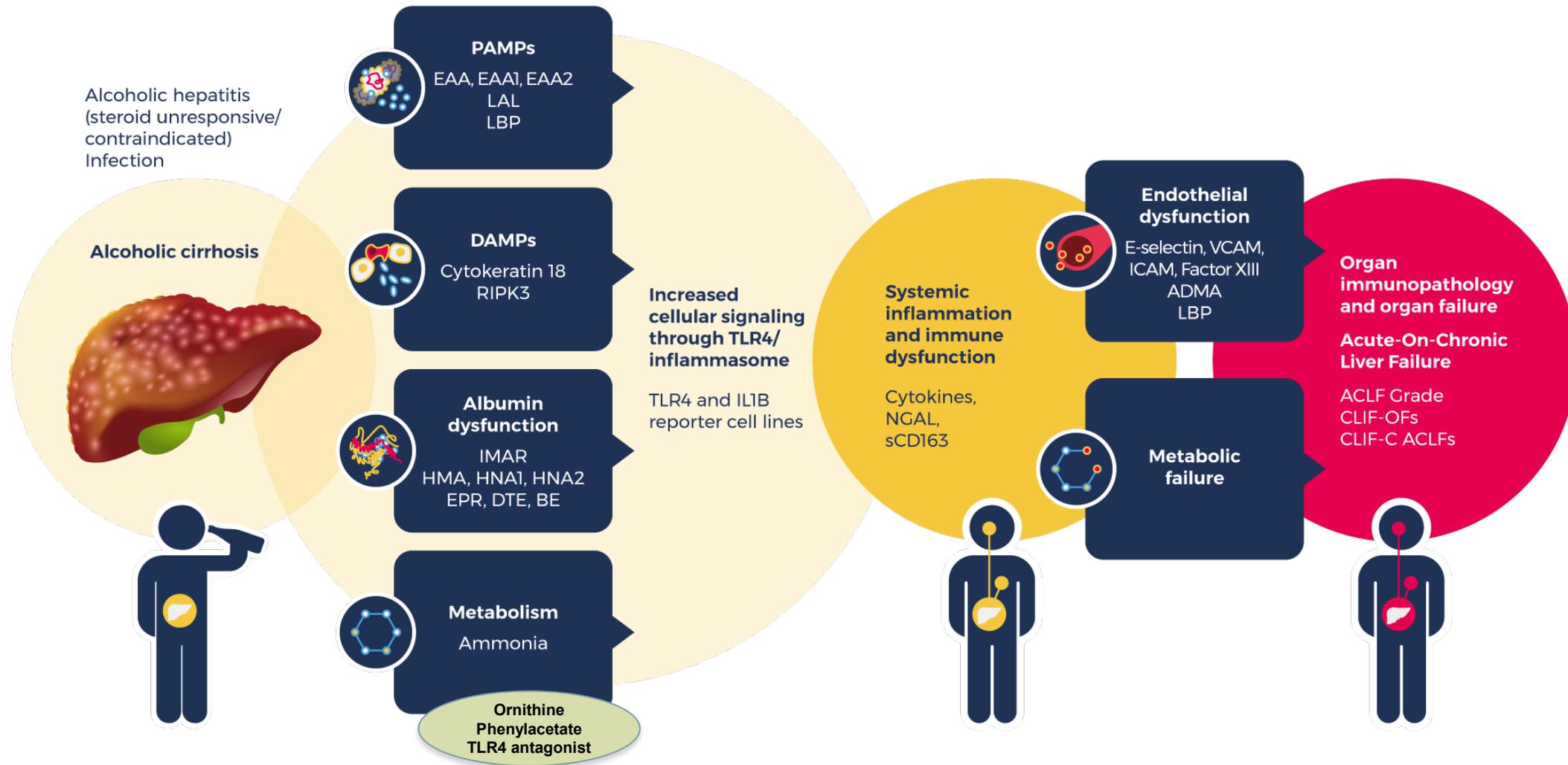
# The pathophysiologic model for developing therapies



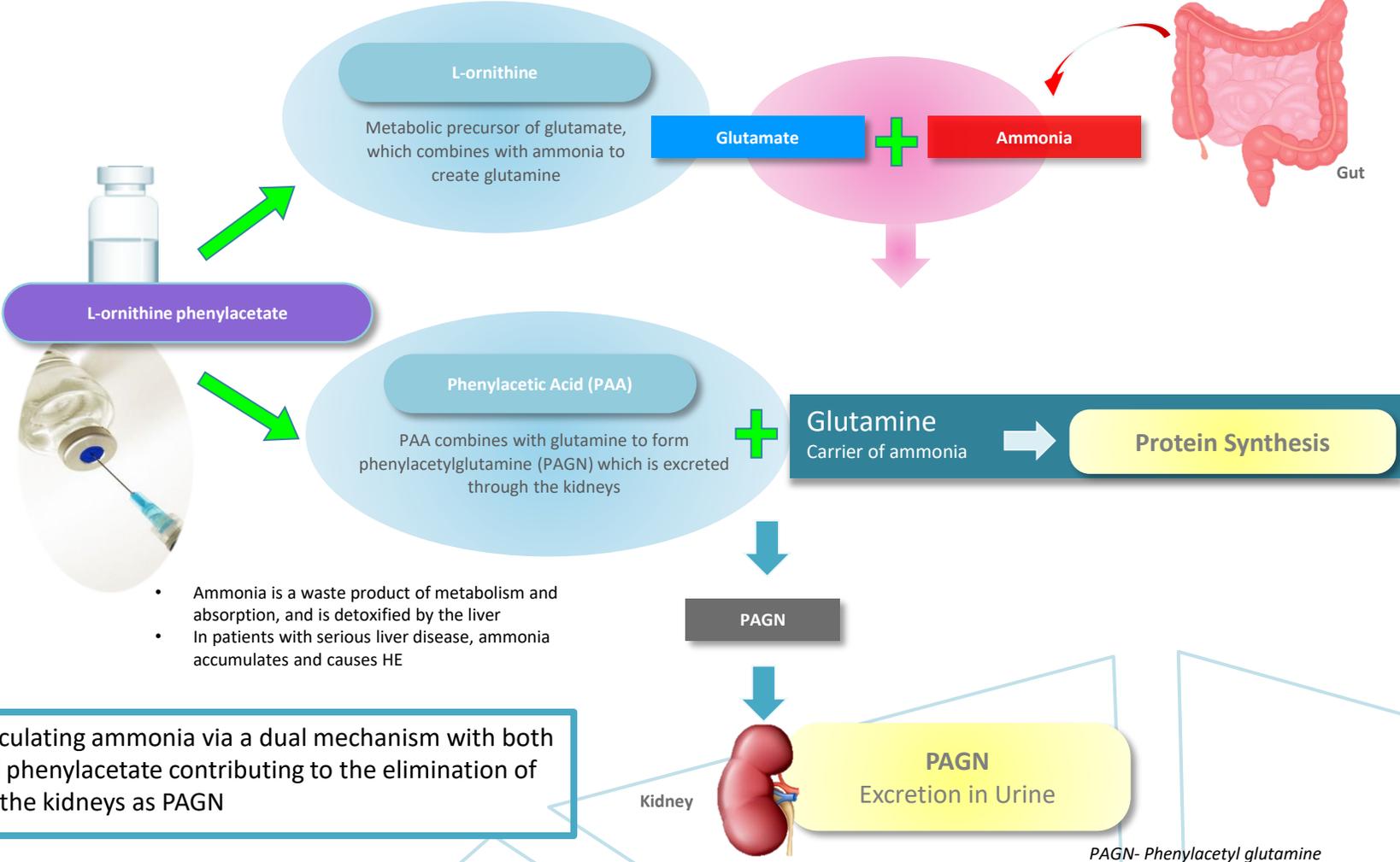
# New therapies under development



# New therapies under development



# Novel mechanism of action that helps to eliminate ammonia in the bloodstream

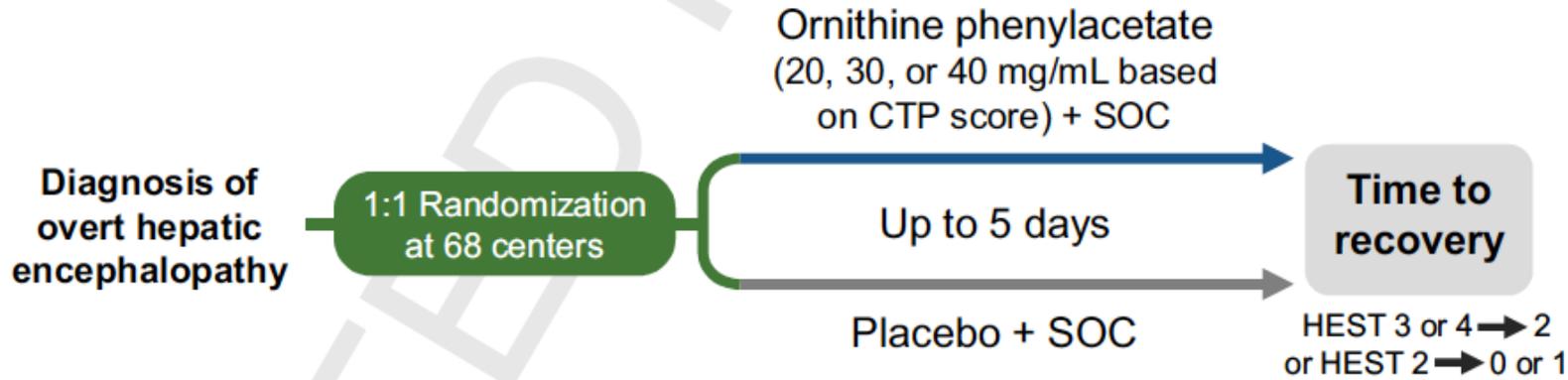


Eliminates circulating ammonia via a dual mechanism with both ornithine and phenylacetate contributing to the elimination of ammonia via the kidneys as PAGN

# Efficacy and Safety of Ornithine Phenylacetate for Treating Overt Hepatic Encephalopathy in a Randomized Trial

Robert S. Rahimi,<sup>\*,a</sup> Rifaat Safadi,<sup>‡,a</sup> Dominique Thabut,<sup>§</sup> Kalyan Ram Bhamidimarri,<sup>||</sup> Nikolaos Pyrsopoulos,<sup>¶</sup> Amy Potthoff,<sup>#</sup> Stan Bukofzer,<sup>#</sup> and Jasmohan S. Bajaj<sup>\*\*</sup>

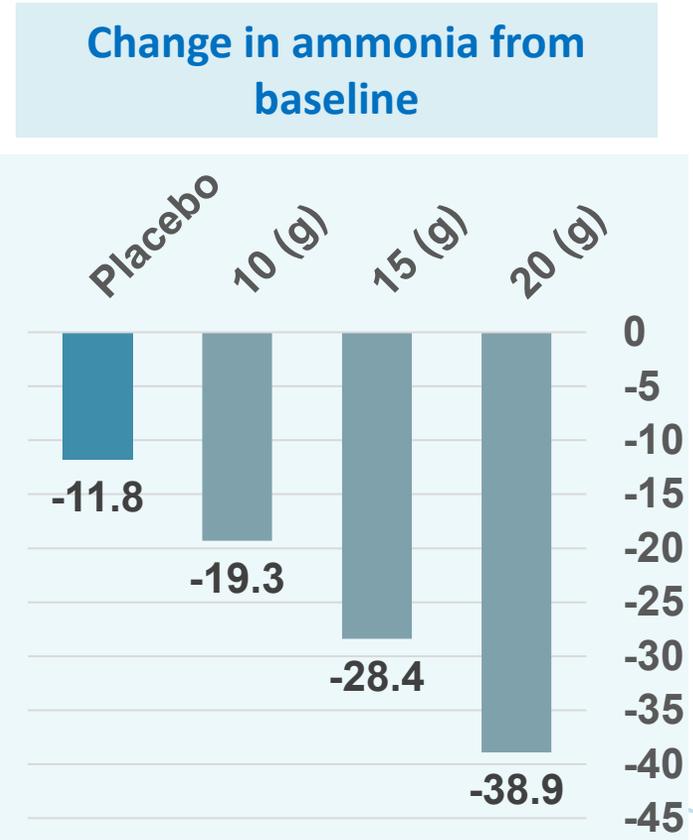
**Phase 3 Trial being organized**



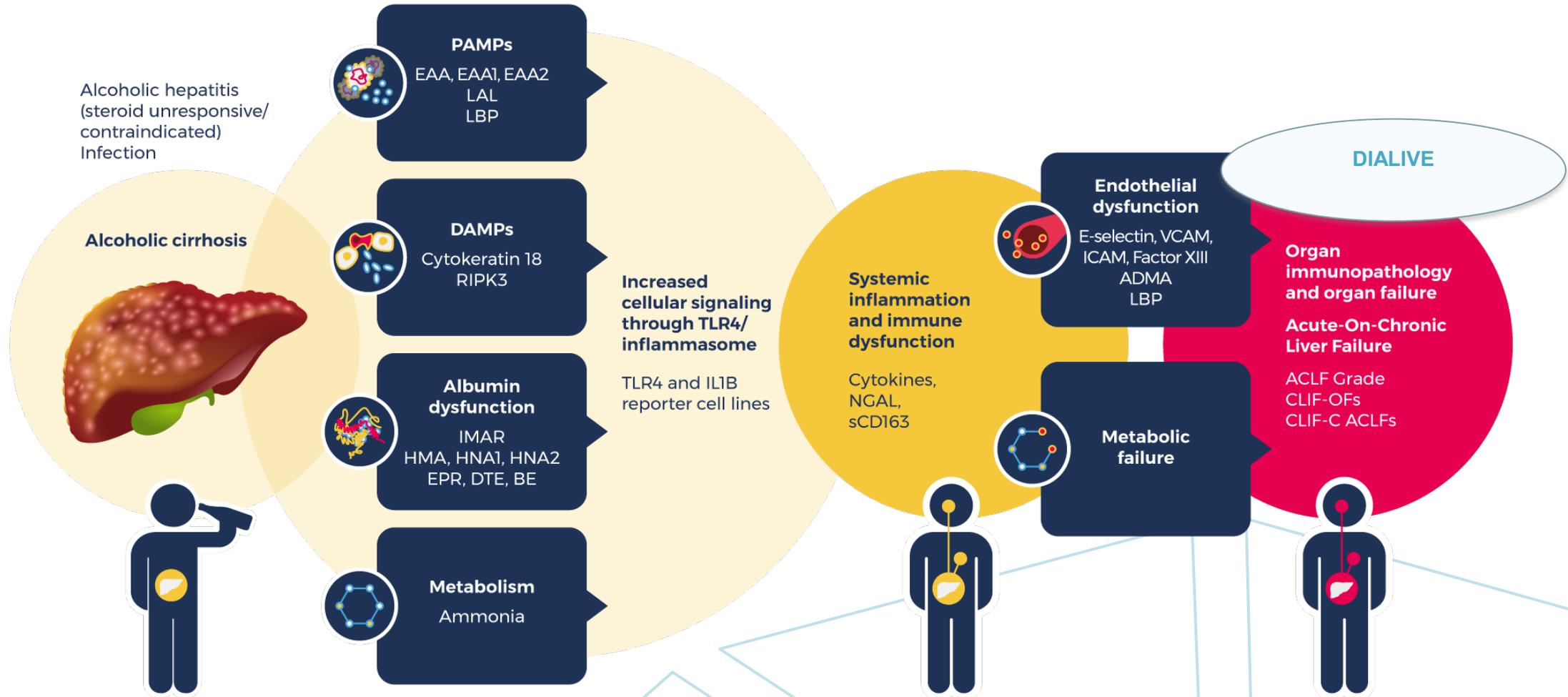
## Time to clinical improvement in OHE by screening NH<sub>3</sub>: OP vs placebo

All patients (N=231) with locally determined screening NH<sub>3</sub> >ULN  
 Median time, 47 vs 64 hours; difference, 17 hours  
 HR (95% CI): 1.249 (.907–1.719); P=.129

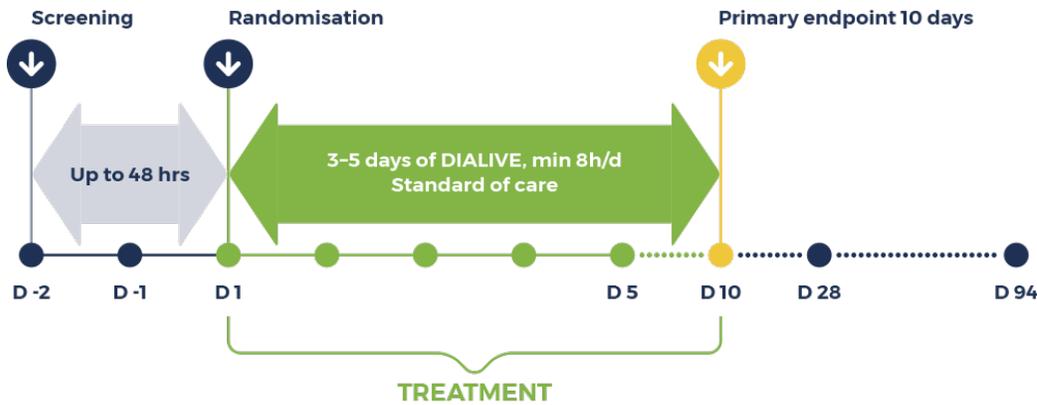
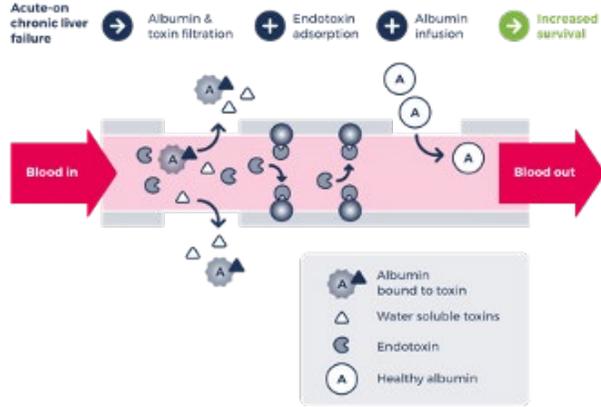
Exploratory analysis (n=201) with centrally determined screening NH<sub>3</sub> >ULN  
 Median time, 42 vs 63 hours; difference, 21 hours  
 HR (95% CI): 1.309 (.939–1.824); P=.034



# New therapies under development



# DIALIVE: Novel Liver Assist Device

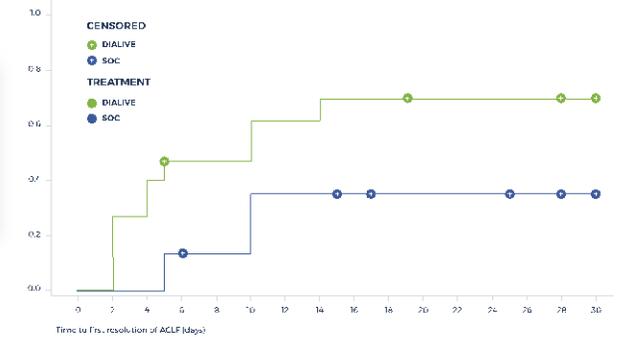


DIALIVE is associated with significantly faster 'time to resolution of ACLF' compared with SOC



Group	Total	ACLF resolved	Time-to-resolution (p25 ; median time)	P-value (Log-rank)
DIALIVE	15	10 (66.7 %)	2 days; 10 days	0.0307
SOC	15	5 (33.3 %)	10 days; not reached	

Survival curves for time to resolution of ACLF



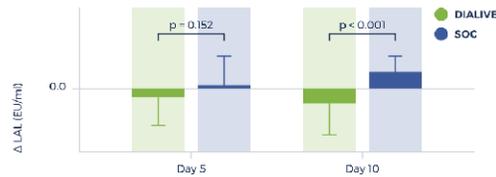
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733057.



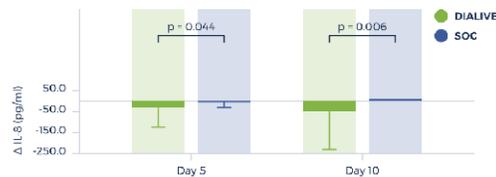
# DIALIVE modifies pathophysiological process involved in the pathogenesis of ACLF



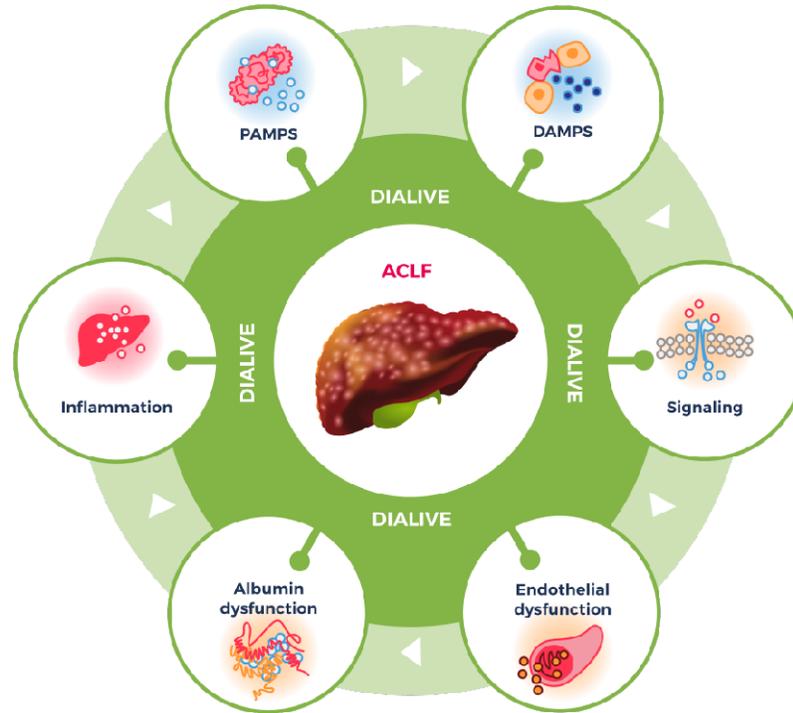
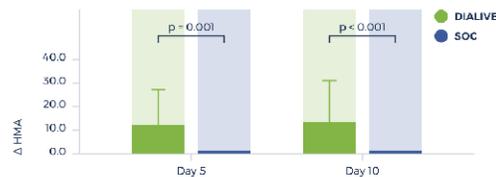
## PAMPS



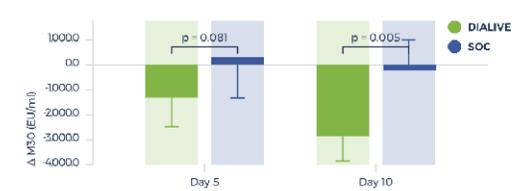
## Systemic inflammation and immune dysfunction



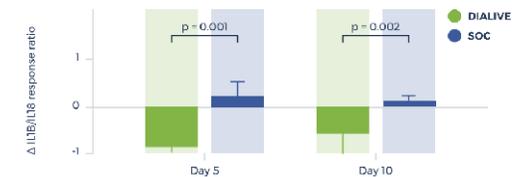
## Albumin dysfunction



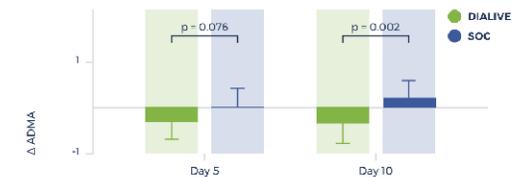
## DAMPS



## Increased cellular signaling through TLR4/inflammasome



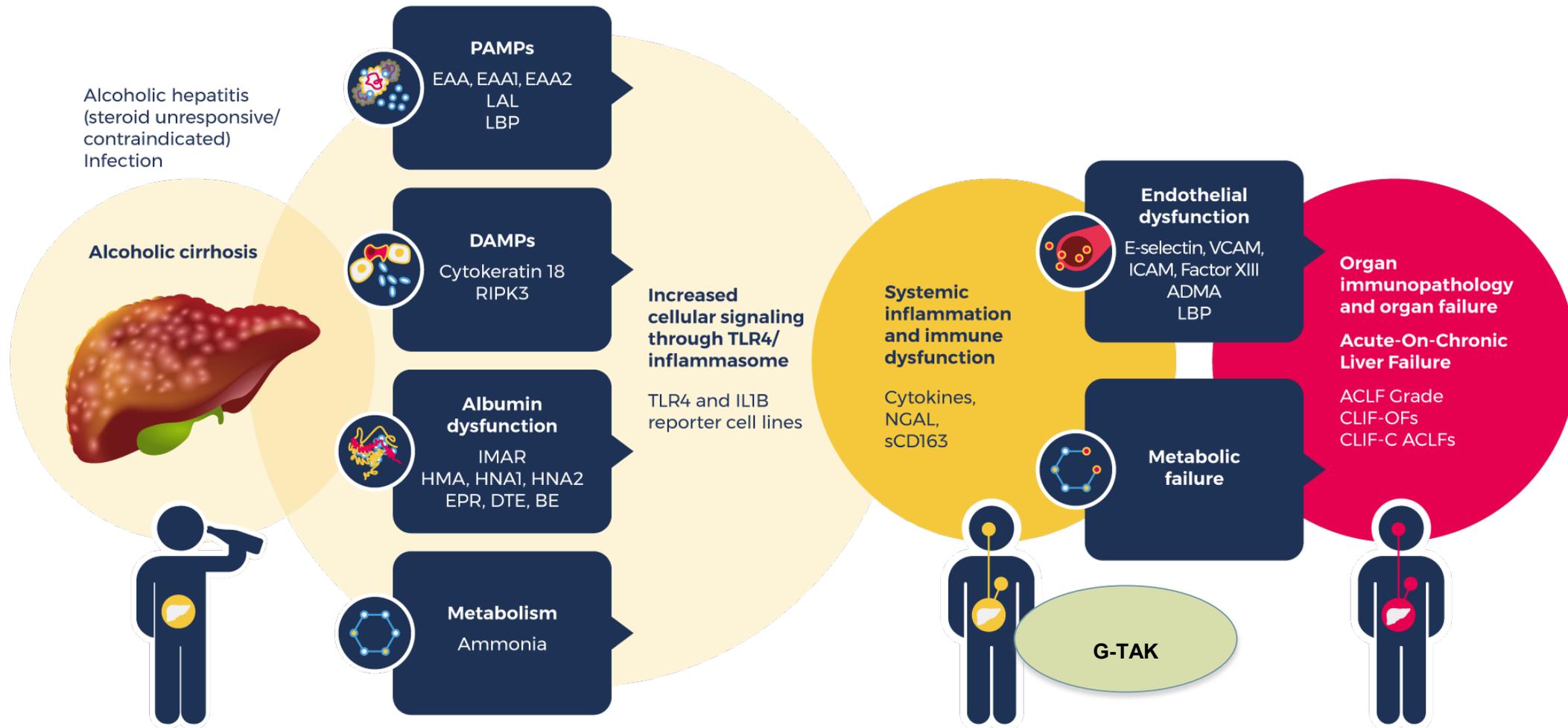
## Endothelial dysfunction



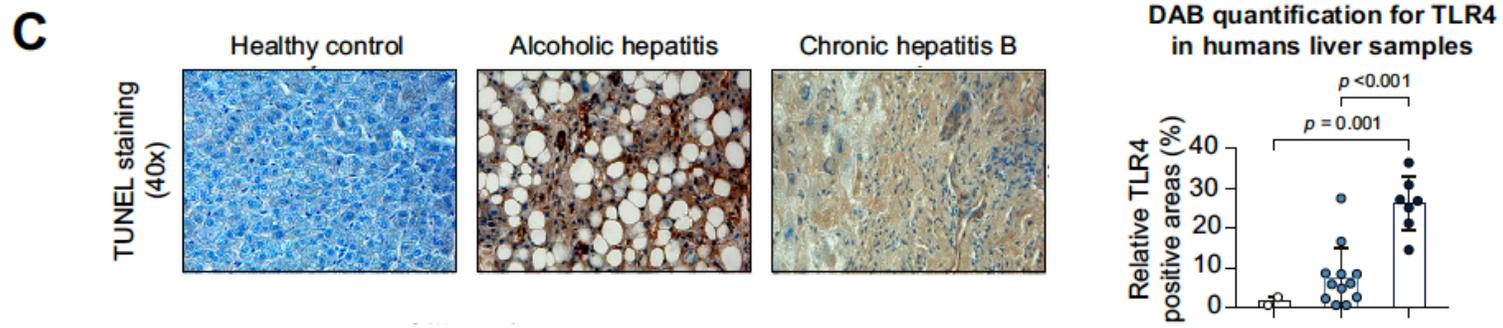
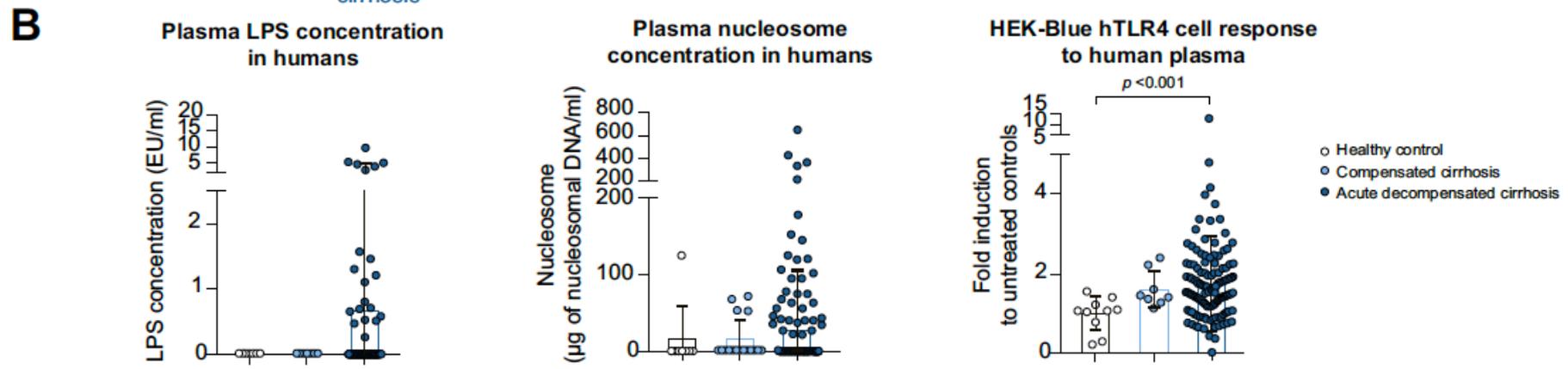
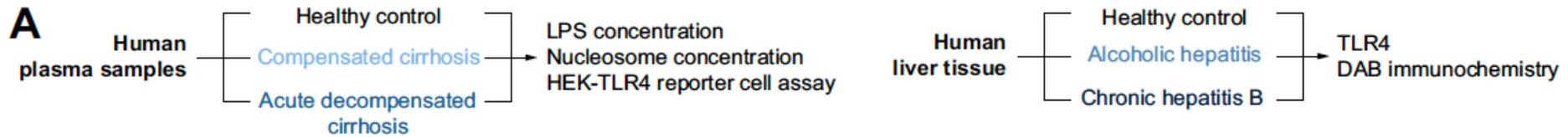
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733057.

# A pivotal study is being planned

# New therapies under development

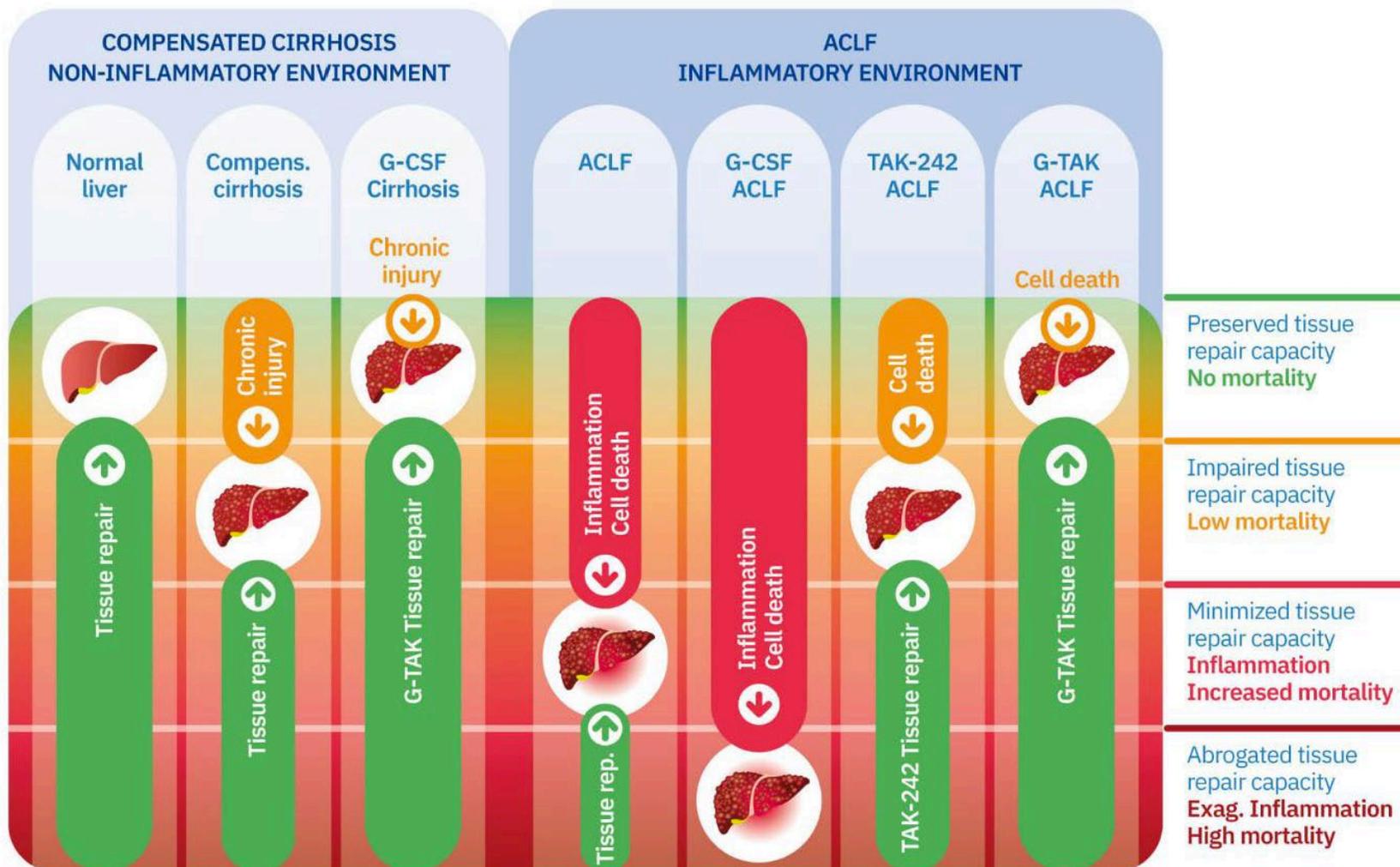


# LPS concentration, TLR4 Ligands and Hepatic TLR4 expression



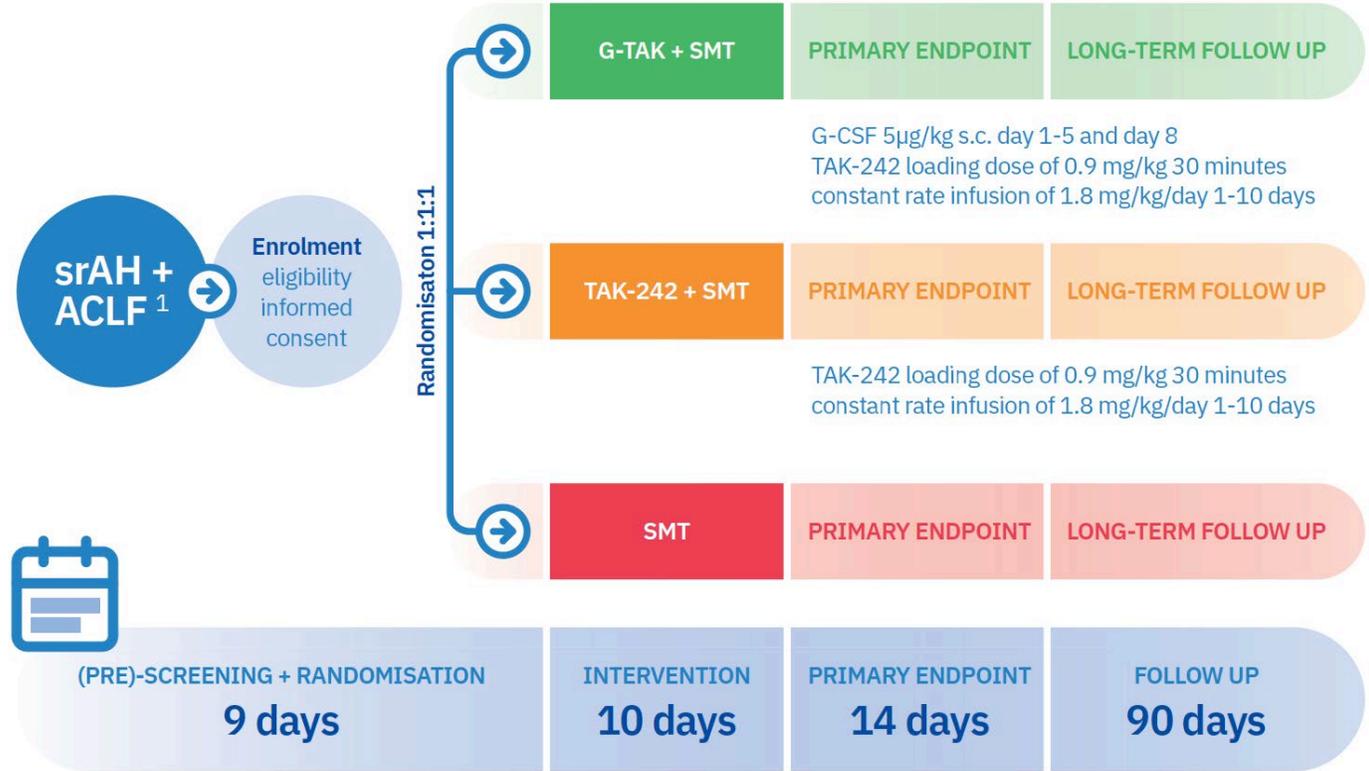
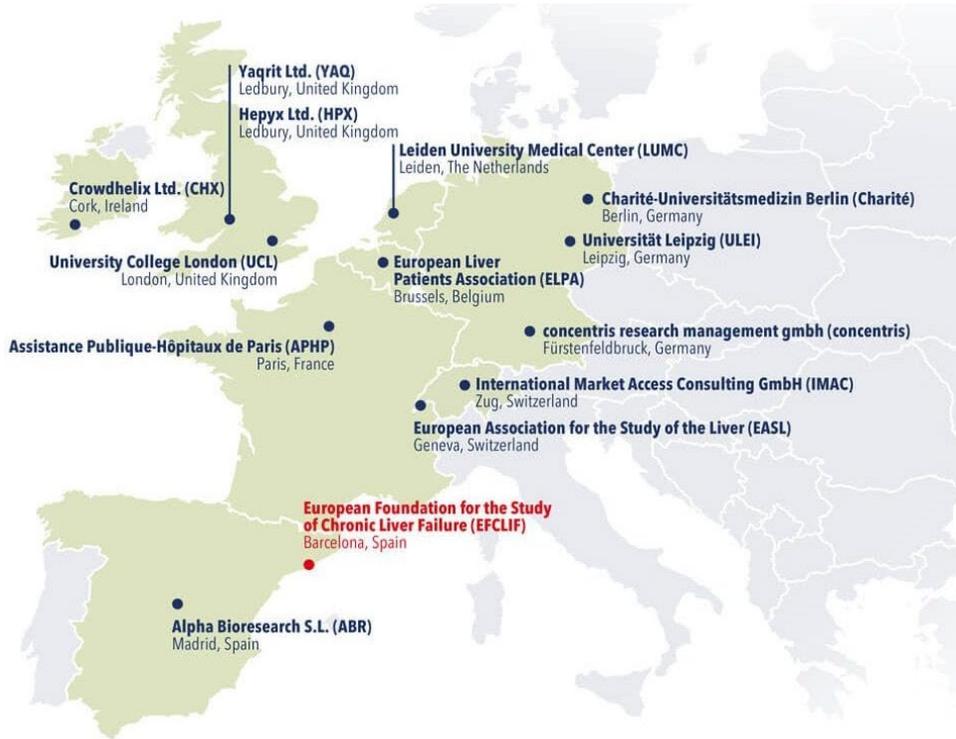
# Combinatorial therapeutic approach to ACLF

## Granulocyte colony stimulating factor + TAK-242 (TLR4 antagonist) G-TAK





# A-TANGO



**SMT:** Standard medical therapy    **srAH:** steroid resistant alcoholic hepatitis

<sup>1</sup> Jalan R et al. J Hepatol 2014; 61: 1038–1047 – ACLF grade 1–3, maximum 3 organ failure and no hepatic encephalopathy grade 3/4



## EF Clif

EUROPEAN FOUNDATION FOR THE STUDY OF CHRONIC LIVER FAILURE





- ACLF and CLIF Consortium: Re-classifying Acute Decompensation and ACLF
- Changing the pathophysiological paradigm of decompensated cirrhosis
- Developing new therapies in the ACLF space
- **1<sup>st</sup> smell of therapeutic success: Liver Transplantation – The CHANCE study**
- Prevention of ACLF and its recurrence

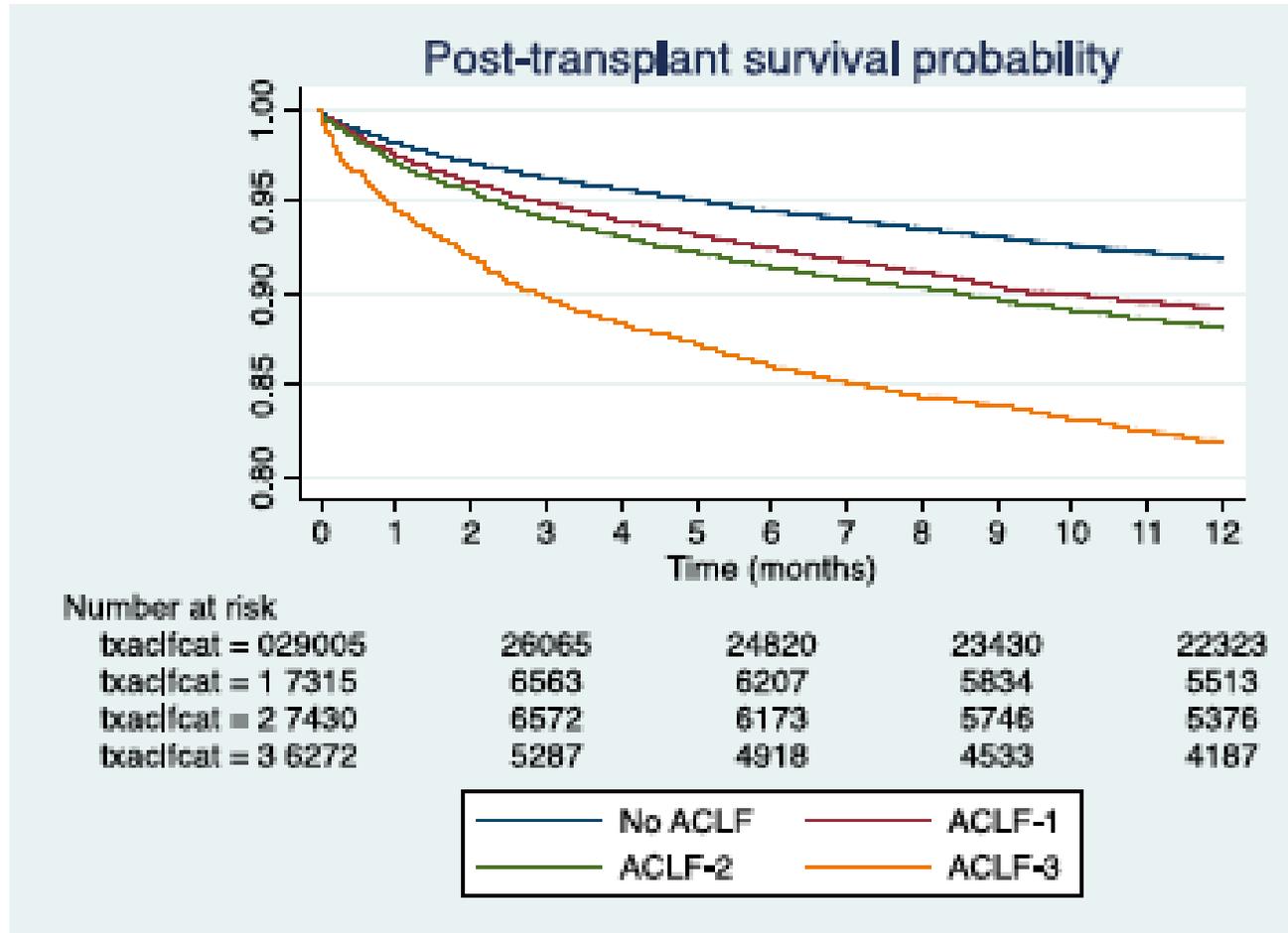
# Factors Associated with Survival of Patients With Severe Acute-On-Chronic Liver Failure Before and After Liver Transplantation



Vinay Sundaram,<sup>1,\*</sup> Rajiv Jalan,<sup>2,\*</sup> Tiffany Wu,<sup>3</sup> Michael L. Volk,<sup>4</sup> Sumeet K. Asrani,<sup>5</sup> Andrew S. Klein,<sup>6</sup> and Robert J. Wong<sup>7</sup>

## UNOS database: 2005-2016

ACLF 0: 29,283  
 ACLF 1: 7375  
 ACLF 2: 7513  
 ACLF 3: 6381



# Risk factors high mortality rates after liver transplantation in severe ACLF

- Age > 60yr
- Severe co-morbidities
- ARDS (PaO<sub>2</sub>/FiO<sub>2</sub> ratio <150)
- High vasopressor
  - Norepinephrine dose >1 lg/kg/min
- Severe lactatemia (>9 mmol/L)
- Infection: Uncontrolled / Fungal / Multidrug resistant
- Time on the waiting list
- Transplantation using marginal organs

## TAM Score (Europe)

- *Lactate*
- *Pao<sub>2</sub>/Fio<sub>2</sub> ratio*
- *Age*
- *White cell count*

## \*SALT score (US)

- *Age*
- *Diabetes*
- *Resp Failure*
- *Inotropes: Single/double*
- *BMI*

Artzner et al. AJT 2020  
\*in review

# Many unanswered questions

- Lack of intention-to-treat results from the time of wait listing
- Detailed information about waiting list outcomes
- Best organ allocation system for this specific population
- Objective limits to define futile LT
- Ideal timing
- Characteristics of donor organ to ensure acceptable post-LT outcomes
- Long-term post-LT survival rates and impact on the quality of life (QoL)
- Resource utilization of performing LT and
- The overall results across the different continents



# The CHANCE study

## Study design

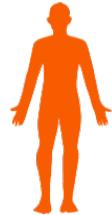
Prospective non-interventional observational global study



INTERNATIONAL LIVER  
TRANSPLANTATION SOCIETY



ELITA  
European  
Liver and Intestine  
Transplant Association



**Group 1**  
ACLF 2-3



Pre-  
screening



LT team  
referral



No limit for group 1  
patients on waiting list



Screening inclusion



**Group 2**  
No ACLF / ACLF 1



Group 2 patients can be  
up to 3 months on waiting  
list before inclusion



Screening inclusion:  
Group 2 developing ACLF 2-3 on  
waiting list can be included as group 1



MELD >20  
MELD >20 when added  
to waiting list



Screening inclusion:  
Group 2 on waiting list must  
be MELD >20 at inclusion

● ● Patients receiving liver transplant



**Group 3**  
ACLF 2-3



Pre-  
screening



LT team  
referral



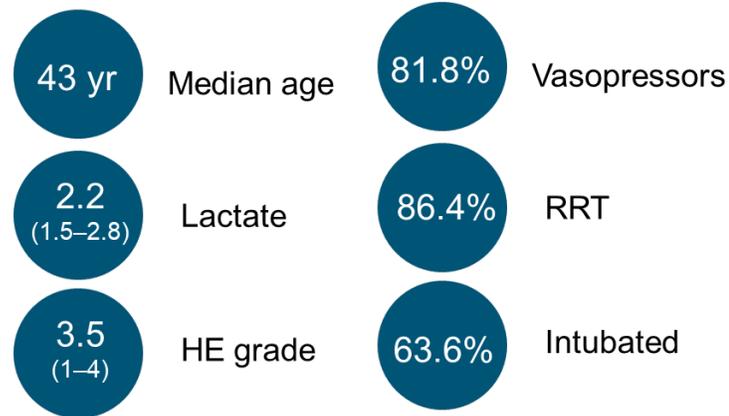
Non-listed



Screening inclusion



# Service development evaluation to transplant ACLF with priority using ACLF-specific criteria (May 2021)



**22 ACLF-3 registrations \***  
on the elective liver transplant list  
26 May 2021–8 April 2022



\* 23 cases received. 1 case rejected (transplanted later via NLOS and currently alive)



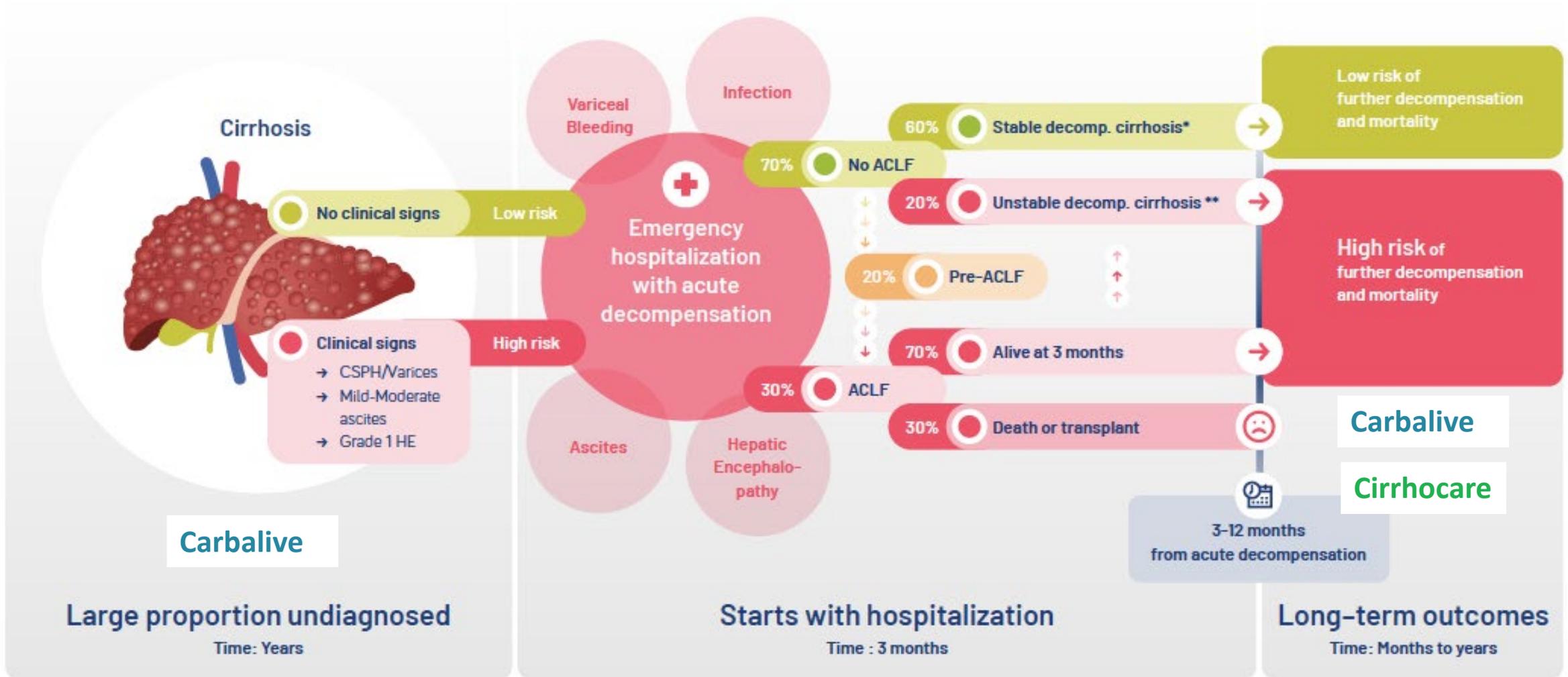
**16/18 patients alive**  
at last follow-up





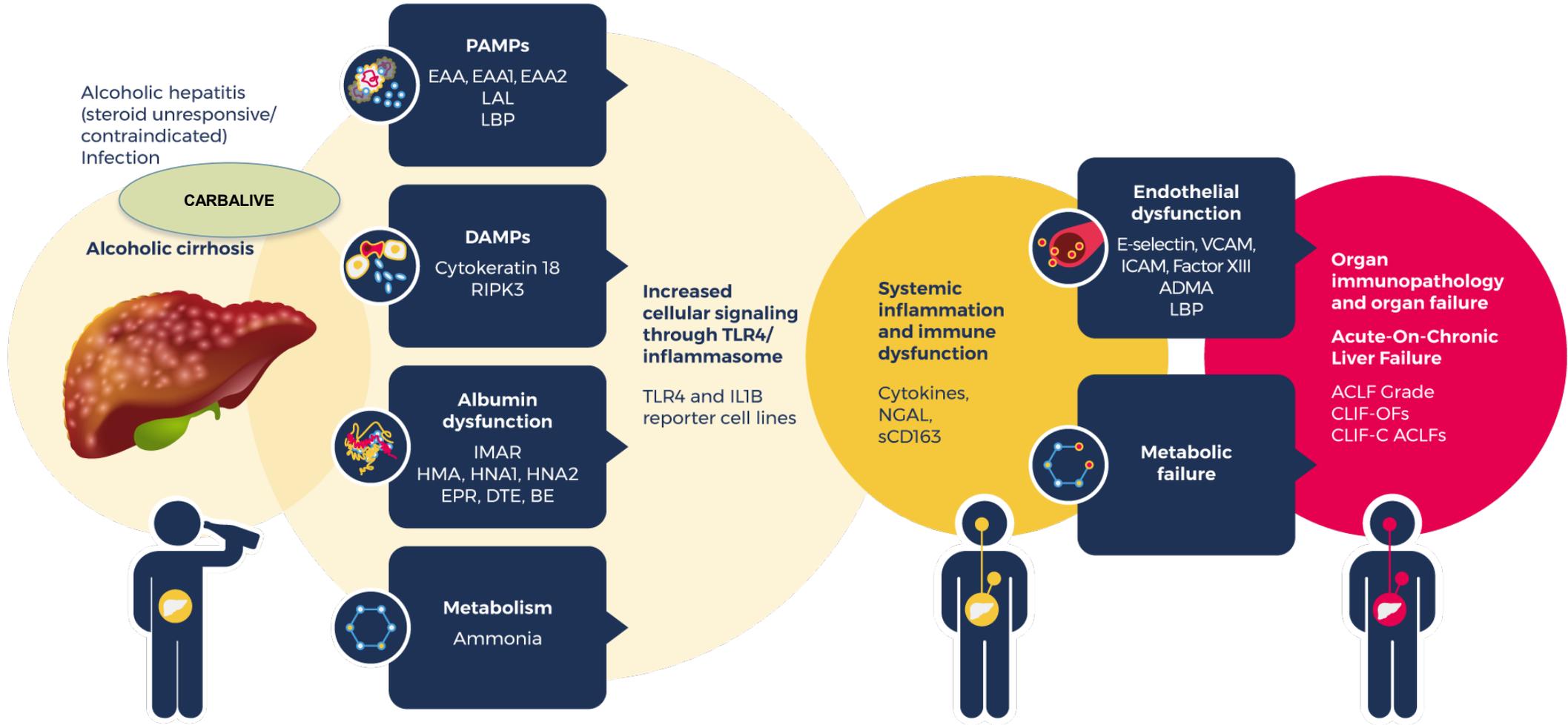
- ACLF and CLIF Consortium: Re-classifying Acute Decompensation and ACLF
- Changing the pathophysiological paradigm of decompensated cirrhosis
- Developing new therapies in the ACLF space
- 1<sup>st</sup> smell of therapeutic success: Liver Transplantation – The CHANCE study
- **Prevention of ACLF and its recurrence**
  - **CARBALIVE**
  - **CirrhoCare**

# Novel therapies under development



\* Stable Decomp Cirrhosis: 100% Survival over 3-months \*\* Unstable Decomp Cirrhosis: 70% Survival over 3-months \*\*\* pre ACLF: 50% Survival over 3-months  
 CSPH: Clinically significant portal hypertension

# Prevention of ACLF and recurrence of complications



# Product Overview - CARBALIVE

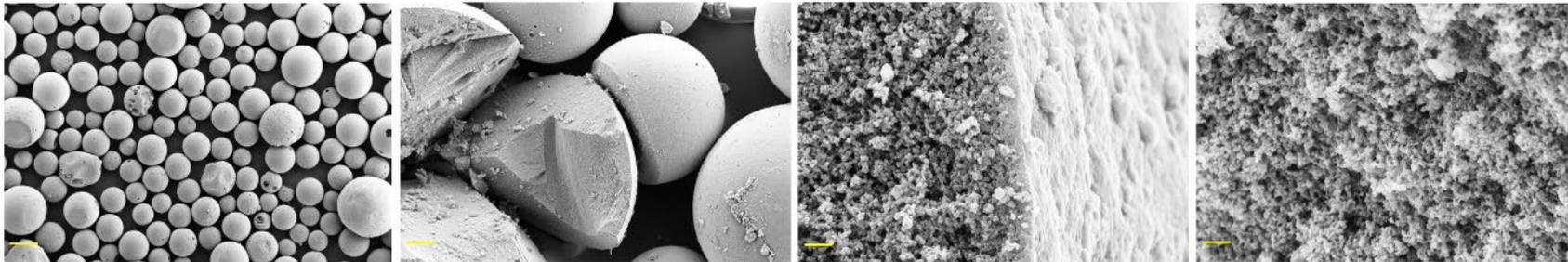
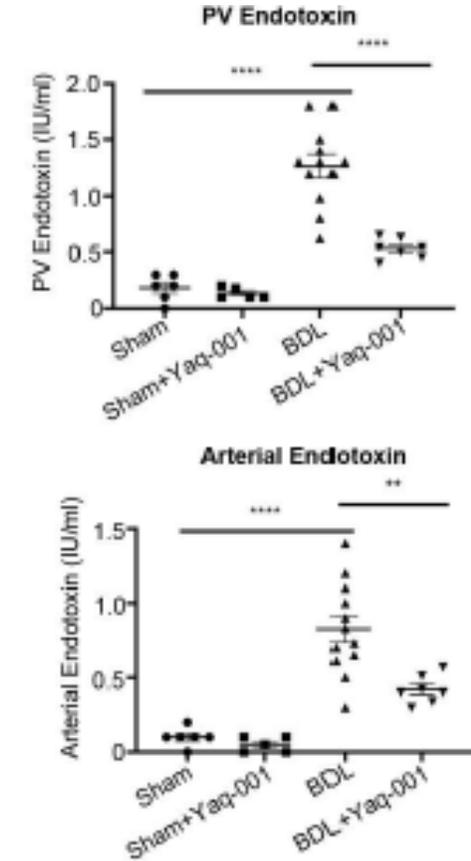
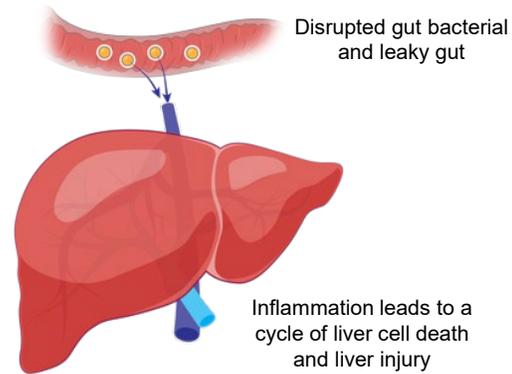
Adsorbent beads whose unique physical structure gives functionality to remove macromolecules such as endotoxins

## Overview

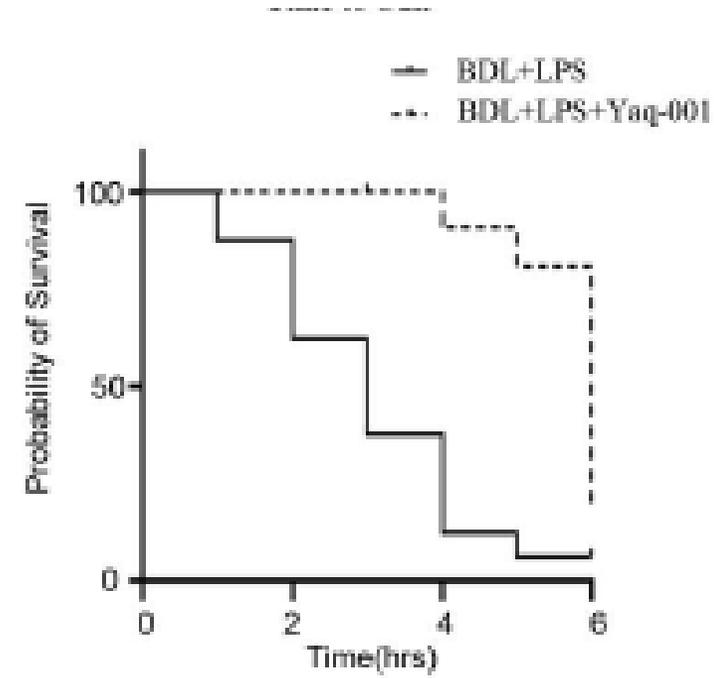
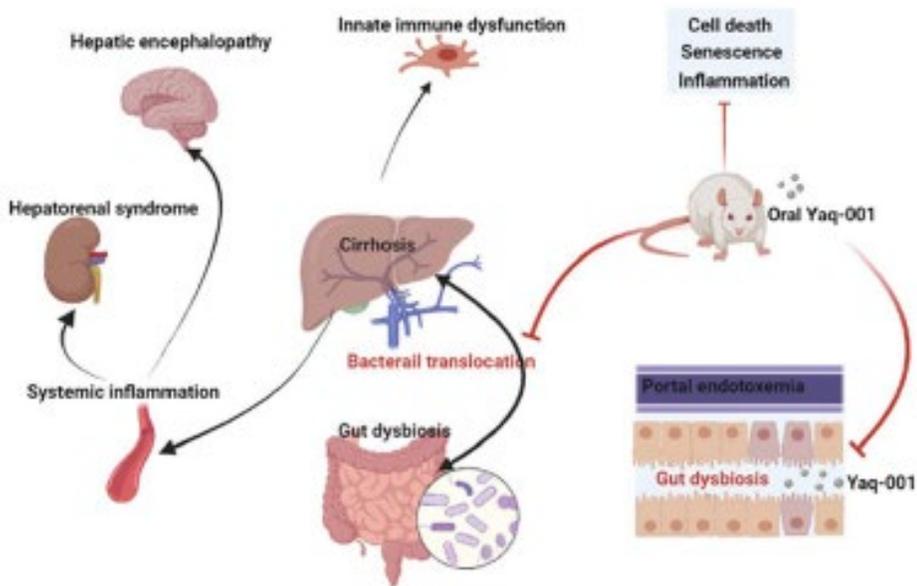
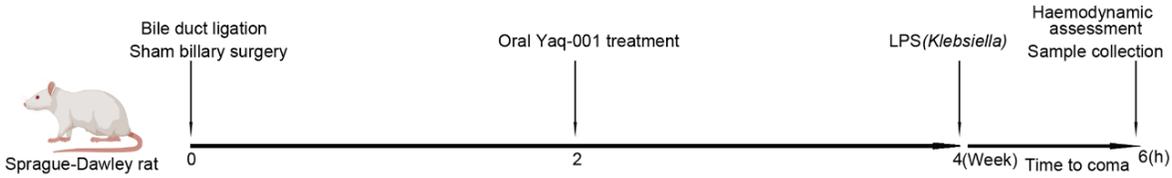
- Carbalive is carbon beads that are unique in physical structure and deliver a different biological performance from traditional adsorbents
- **Manufacturing in own plant creates macropores** (~100nm in diameter) to enable access for large molecules like LPS to 1500 sqm/gram internal surface area.
- Impacts all the pathophysiological factors associated with decompensated cirrhosis
- Can be used at home or outpatient

## How it works

- Carbalive is designed to remove endotoxins (LPS), reduce inflammation and improve gut health



# In animals with cirrhosis CARBALIVE impacts on all multiple organ function and reduces risk of development of ACLF



# Phase 2: Safety, Tolerability and pathophysiological effects (n=28) Randomised Double Blind Clinical Trial in Compensated Cirrhosis

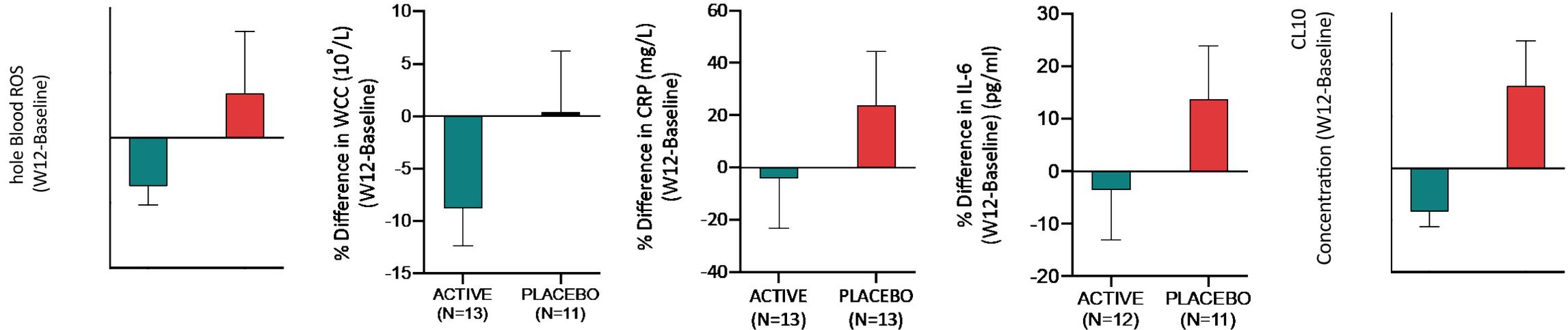
Constitutive Whole Blood ROS

White Blood Cell Count

C-Reactive Protein

Interleukin-6

CXCL 10



1. These data are available in the Carbalive Clinical Study Report derived from Tables 11.8.14, 11.8.149, and 11.8.165 in the CSR Appendices. These data were presented in abstracts in the EASL ILC conference 2021. In each case, data set consists of n=13 for Carbalive and n=10 control arm. In each case, the bar charts combine data from all the time points in every patient, if available. The data are combined using a technique called linear mixed modelling in which lines of regression for each patient have a line of regression fitted to them, with highly variable time series given a lower weight. Note: ROS = Reactive oxygen species, which are molecules that are part of the immune system's ability to kill cells. IL-6 = interleukin 6 which promotes inflammation, a central problem in this patient group. Less IL-6 implies less inflammation. CRP = C-reactive proteins, molecules produced in the liver and is at abnormally high levels in many liver disease patients. WWC = White Cell Count. White blood cells increases in response to an infection. Its role in decompensated cirrhosis means that it is part of the CLIF acute decompensation score and so a falling WCC indicates less severe decompensation. CXCL10 = C-X-C motif chemokine ligand 10, is a molecule that is part of the immune system that regulates liver inflammation.

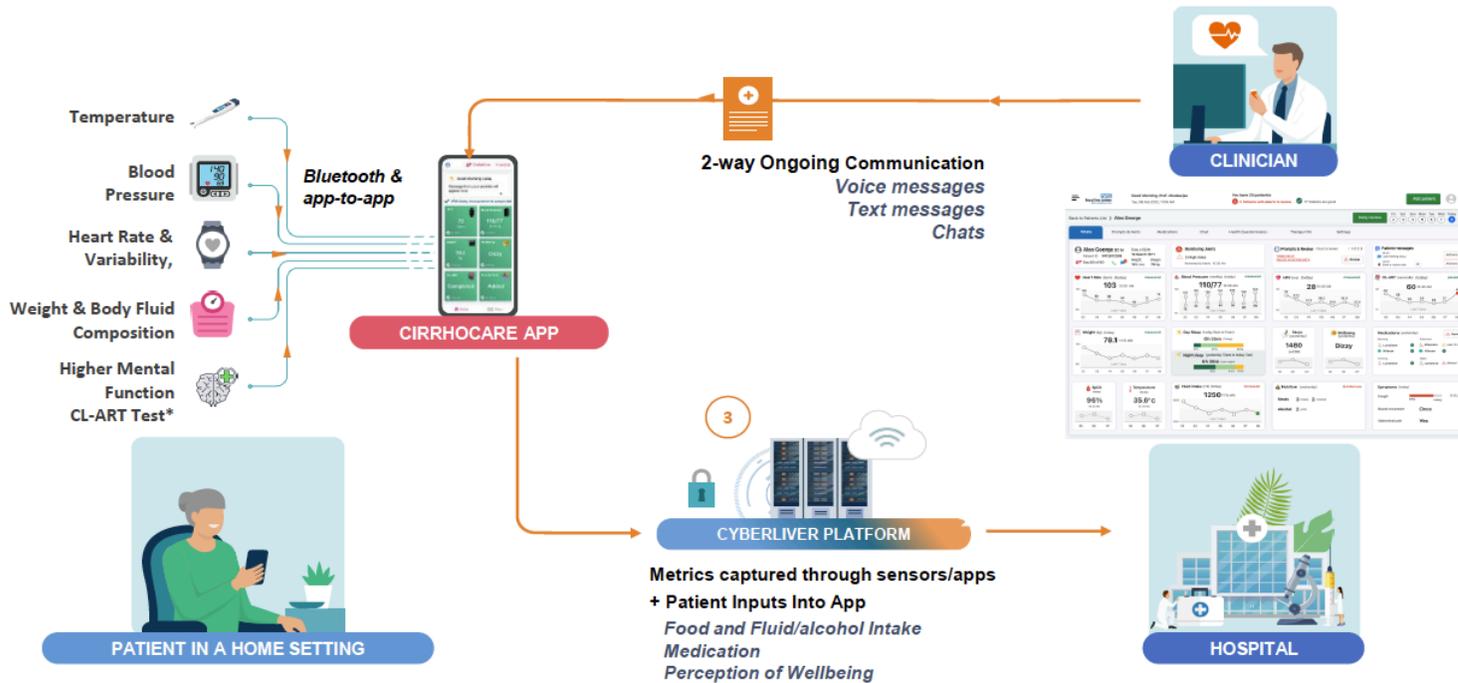
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 634579.



- **A digital therapeutic approach....Cirrhocare®  
([www.cyberliver.com](http://www.cyberliver.com))**

# CirrhoCare provides early diagnosis, allows rapid intervention and reduces hospitalization

## CirrhoCare: decompensated cirrhosis management in the community



## CirrhoCare pathway outcomes from Pilot Study

- 38% reduction in hospital admissions
- 69% reduction in ITU length of stay in days
- 83% reduction in number of unplanned large volume paracentesis
- 83% CirrhoCare enabled early interventions
- 85% patient engagement
- Improved Quality of Life



# Summary

- Clinical characterisation of ACLF has re-classified cirrhosis
- Systemic inflammation and its mediators provide the basis of novel therapies
- Several clinical trials aiming to prevent the occurrence of ACLF, its treatment and prevention of recurrence is underway
- Liver Transplantation is already saving lives and CHANCE study will address unanswered questions
- Digital therapeutic approaches show huge promise as non-pharmacological approach to decompensated cirrhosis



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