

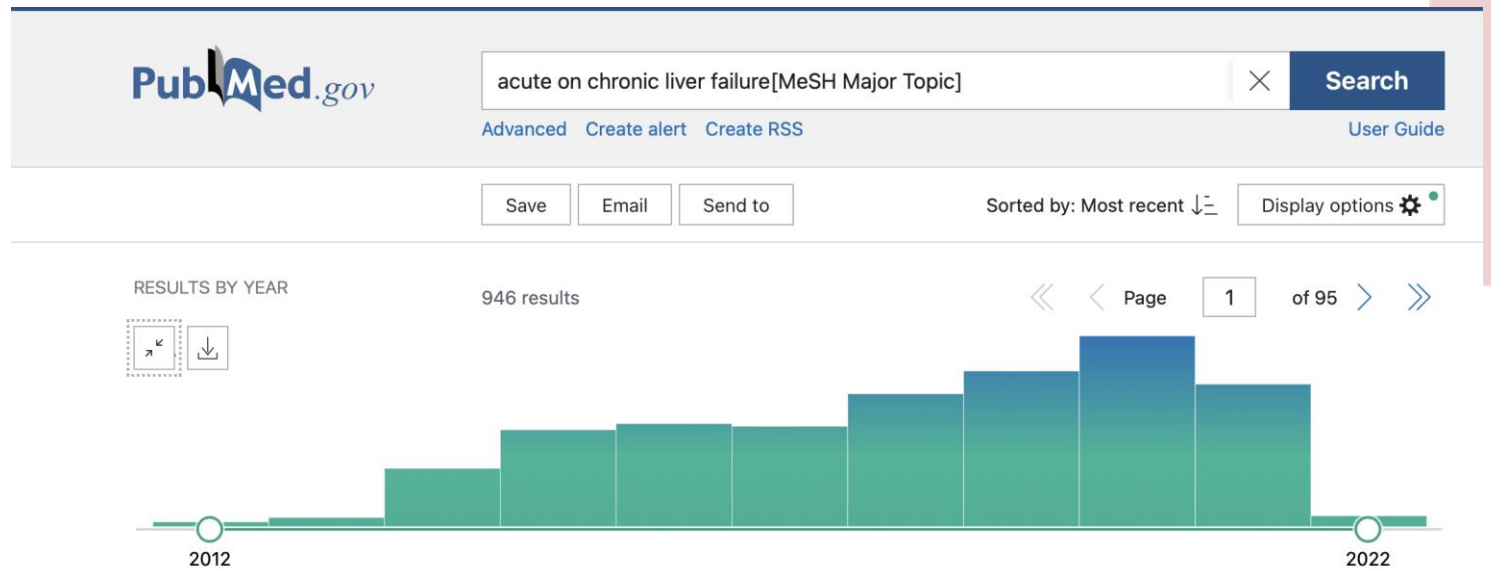


MÁSTER EN HEPATOLOGÍA

UAM Universidad Autónoma de Madrid
Universidad de Alcalá

”Fracaso hepático agudo sobre crónico”

Rafael Bañares



ciberehd



Hospital General Universitario Gregorio Marañón



La presentación habitual del paciente cirrótico avanzado



Diagnóstico del año 2000:
Cirrosis descompensada
Diagnóstico del año 2022:
Acute on chronic liver failure (ACLF)

¿Son cosas distintas?

- El concepto de ALCF
- La patogenia
- La valoración del pronóstico

Cambios en el paradigma clásico de la historia natural de la cirrosis

El concepto clásico

El nuevo paradigma:2022

Dinámica, reversible, bidireccional

Unidireccional

Único e

Limitada al hígado

¿DONDE SE UBICA EN ESTE ESQUEMA EL ACLF?

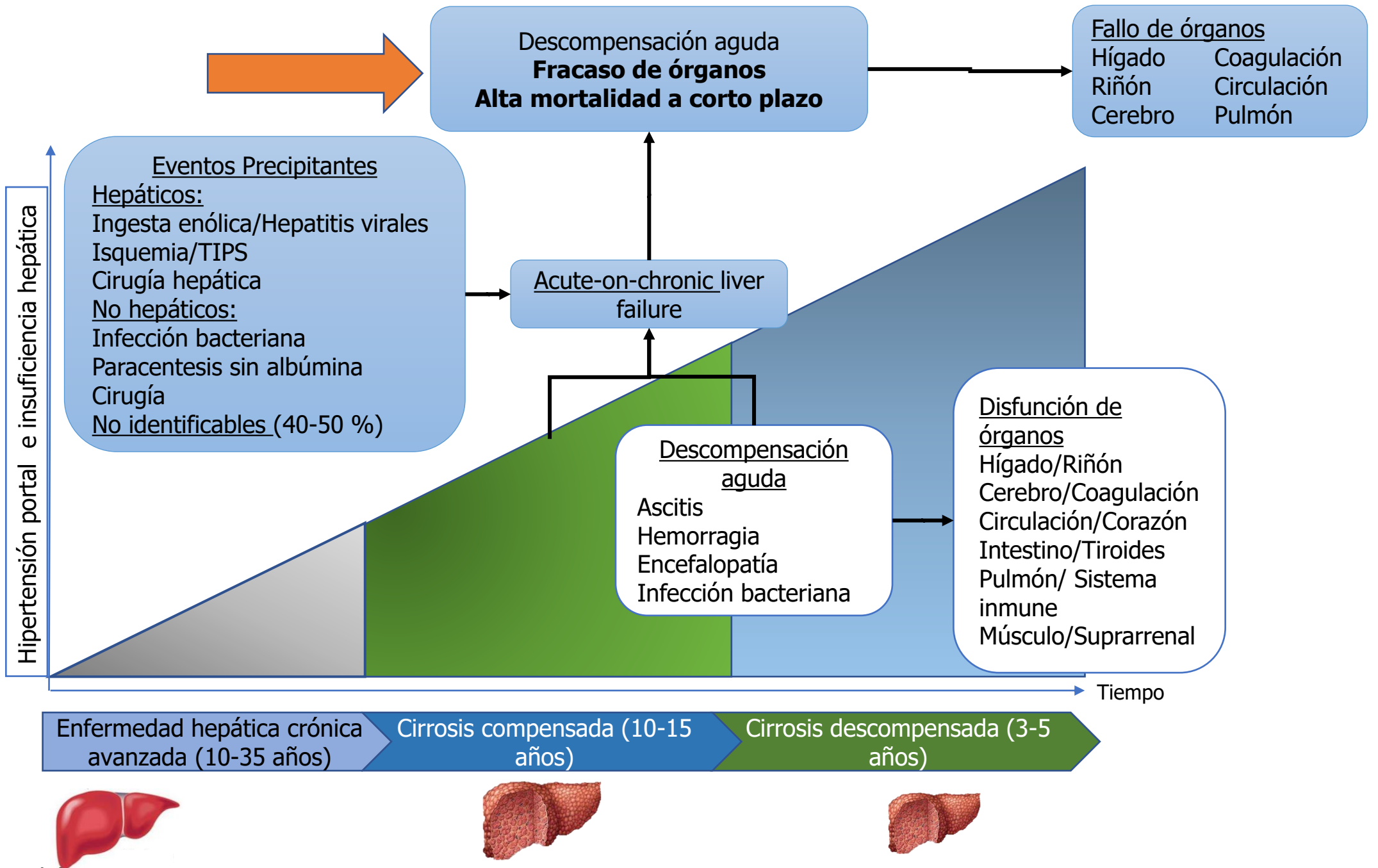
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de riesgo

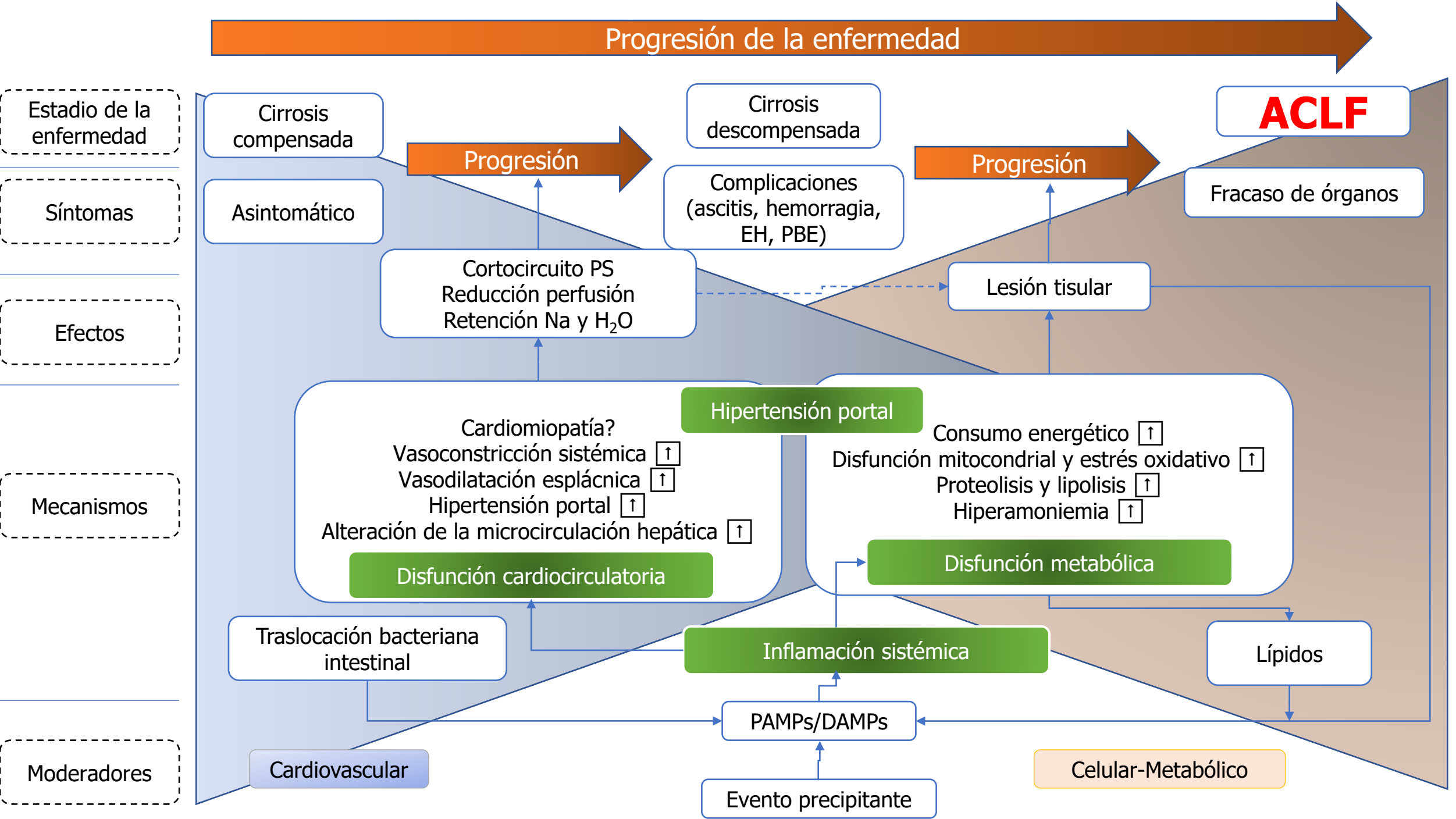
Enfermedad sistémica

Trastorno circulatorio

Participación de otros órganos

Disfunción inmune
Inmunodeficiencia
Inflamación sistémica





Sin embargo, hay diferentes definiciones para ACLF



ASIA



EUROPE



USA

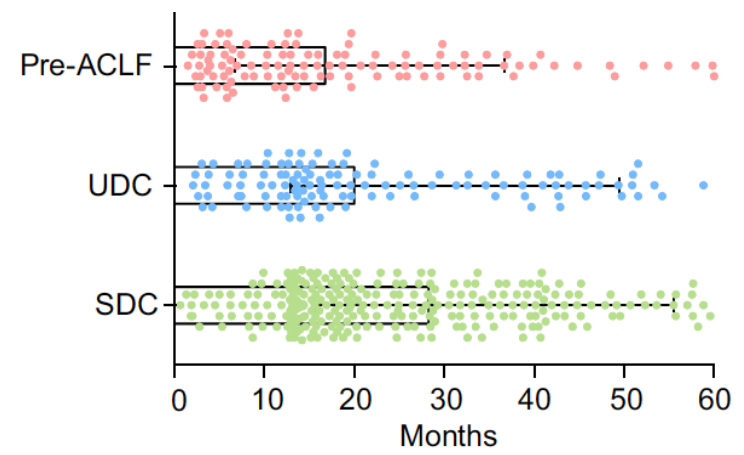
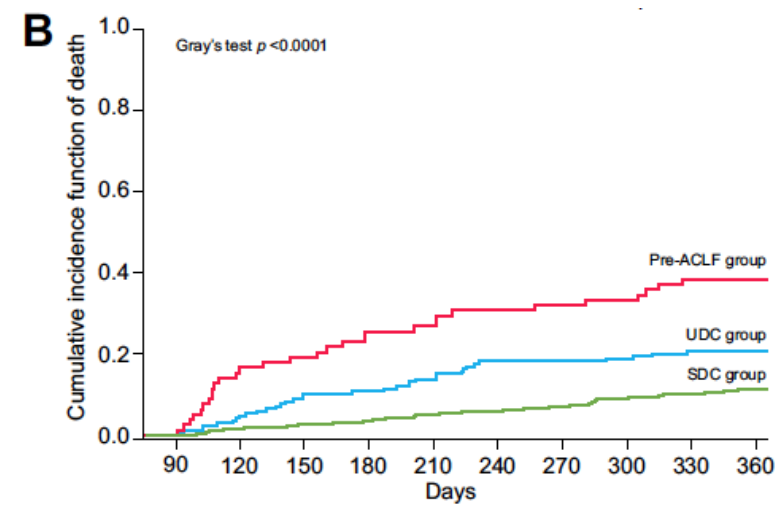
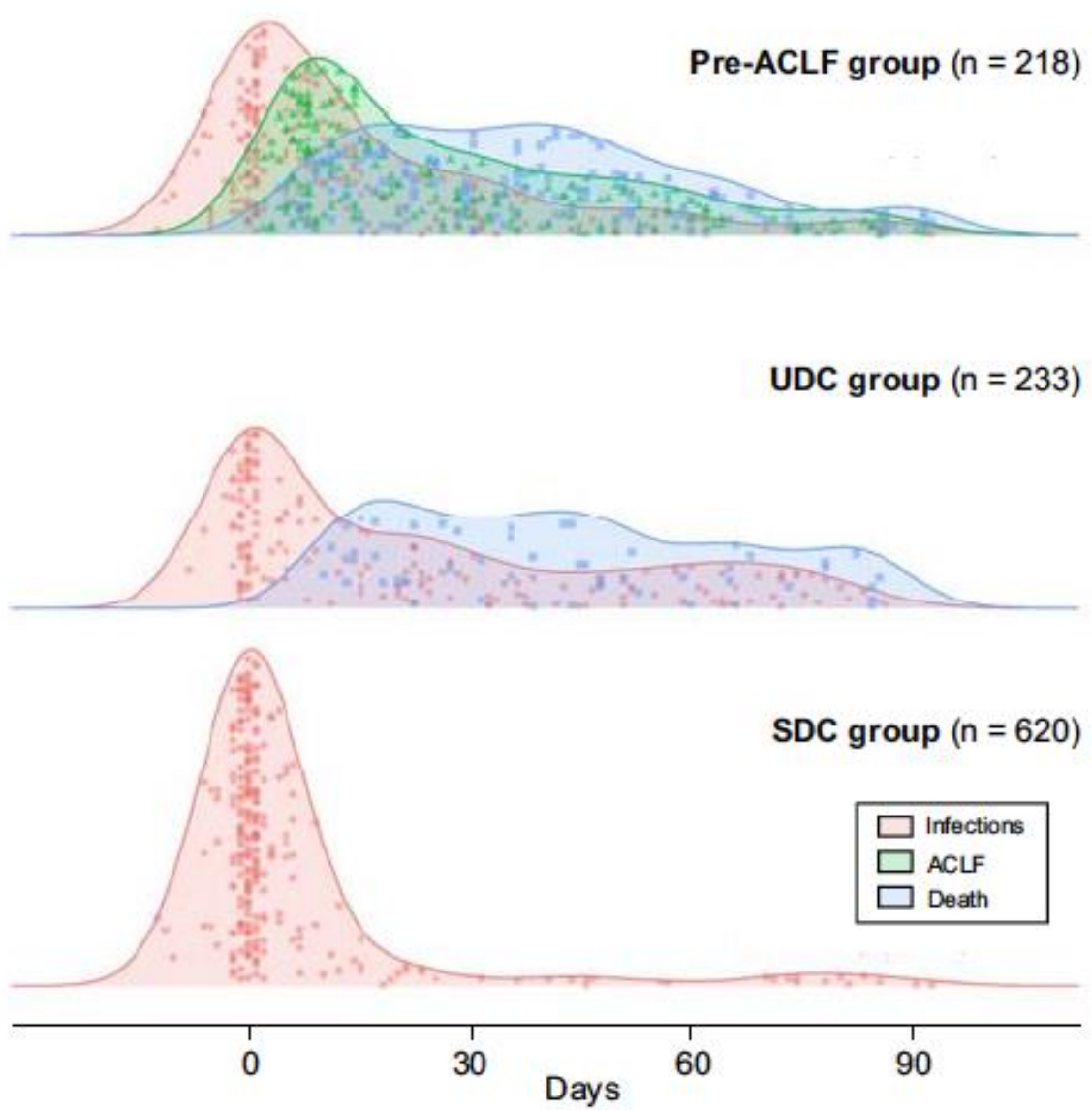
	APASL	EASL-CLIF	AASLD-NACSELD
Derivation	Consensus definition	Prospective observational study (CANONIC study)	Prospective study
Patient population	Chronic liver disease and compensated cirrhosis	Compensated and decompensated cirrhosis	Decompensated cirrhosis
Exclusion	Infection Prior hepatic decompensation	HCC outside Milan criteria HIV infection	HIV infection Prior organ transplantation
Common precipitating events	Reactivation of hepatitis B Superimposed hepatitis E	Alcoholic hepatitis Infection Unknown (40%)	Infection
Requirements for ACLF diagnosis	Ascites, hepatic encephalopathy	Organ failure	Extrahepatic organ failure

The WGO working definition includes four elements

- Population of susceptible patients
 - Patients with chronic liver disease
 - With or without previous diagnosis of cirrhosis
- Need for liver involvement
 - Acute hepatic decompensation
 - Jaundice and prolongation of INR
- One or more extrahepatic failures
- Increased mortality (up to three months)

Which are the requirements of a future ideal ACLF definition?

- Description of a disease clearly distinguishable from chronic liver disease, compensated cirrhosis and traditional decompensated cirrhosis.
- A clearly distinct pathophysiology.
- Ideally, it should have a diagnostic sign, symptom, or confirmatory test.
- The diagnosis of ACLF should be associated to management change.



La presentación habitual del paciente cirrótico avanzado



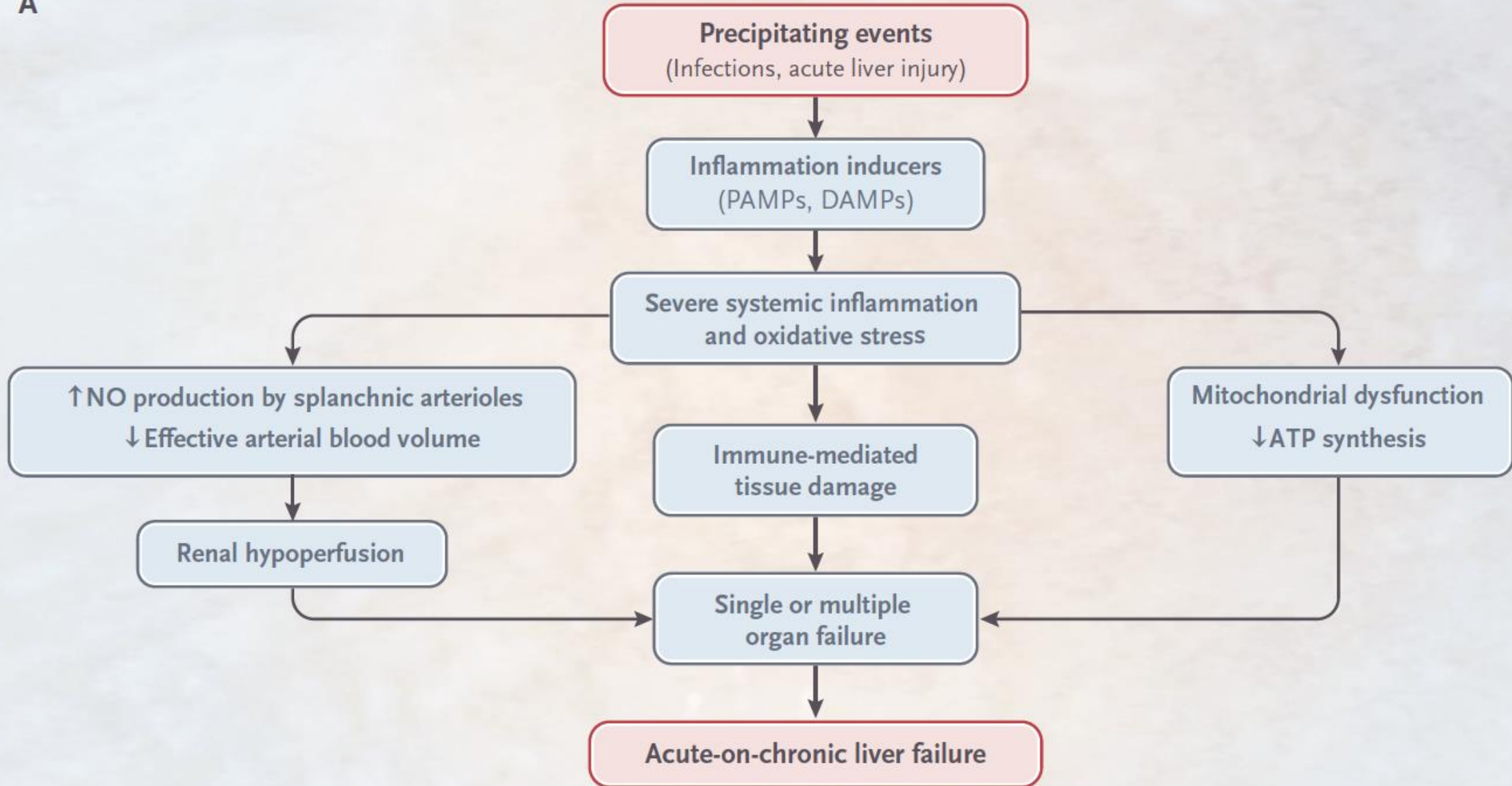
Diagnóstico del año 2000: Cirrosis descompensada
Diagnóstico del año 2021: ACLF

¿Son cosas distintas?

- El concepto de ACLF
- **La patogenia**
- La valoración del pronóstico

Patogenia del ACLF

A

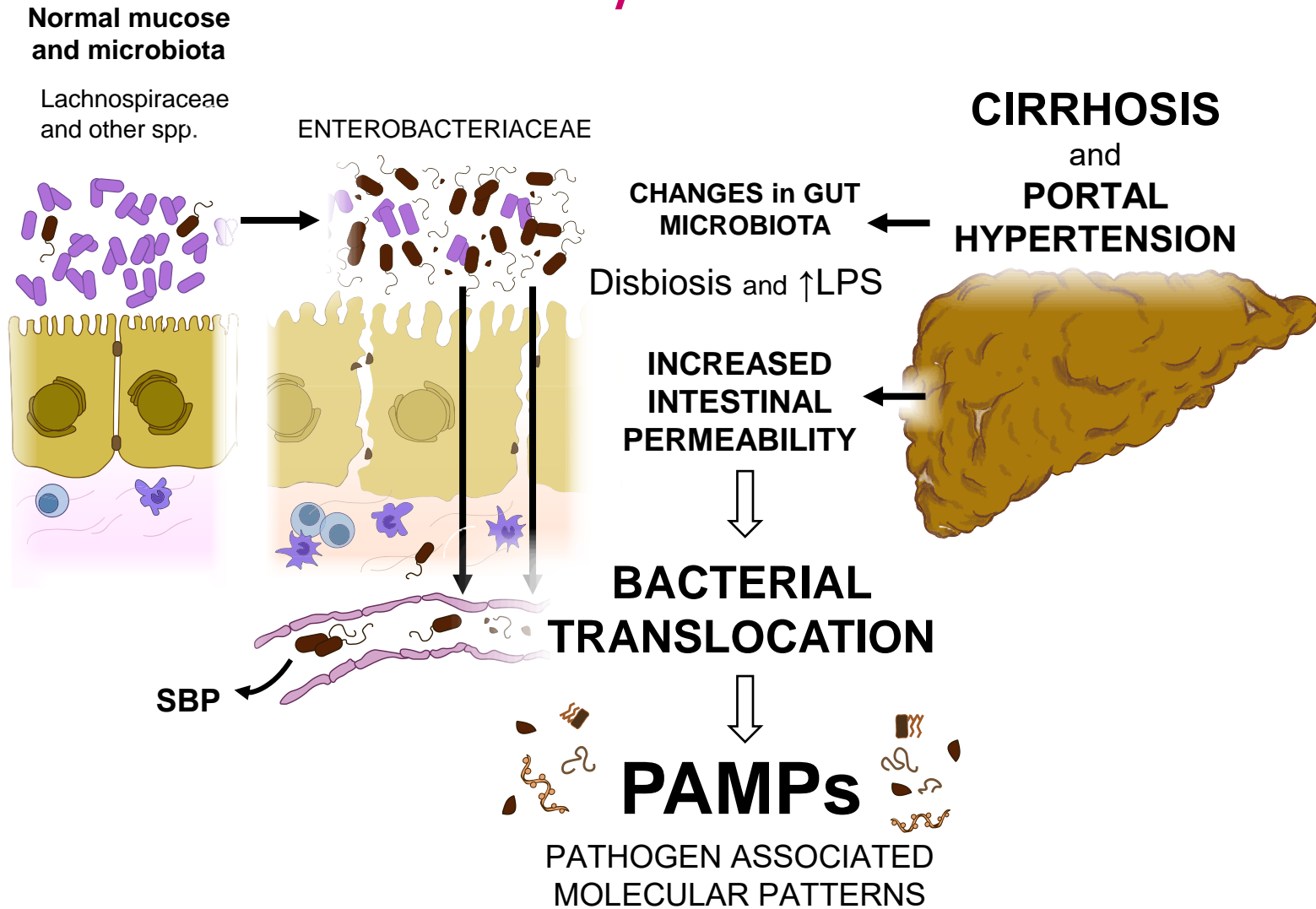


ACLF Pathogenesis: a still uncompleted history with many players

- Inflammation
 - Inducers of inflammation
 - Excessive inflammation
- Inappropriate immune response
- Extension of inflammation to peripheral organs

ACLF Pathogenesis: a still uncompleted history

Chapter 1: Inducers of inflammation



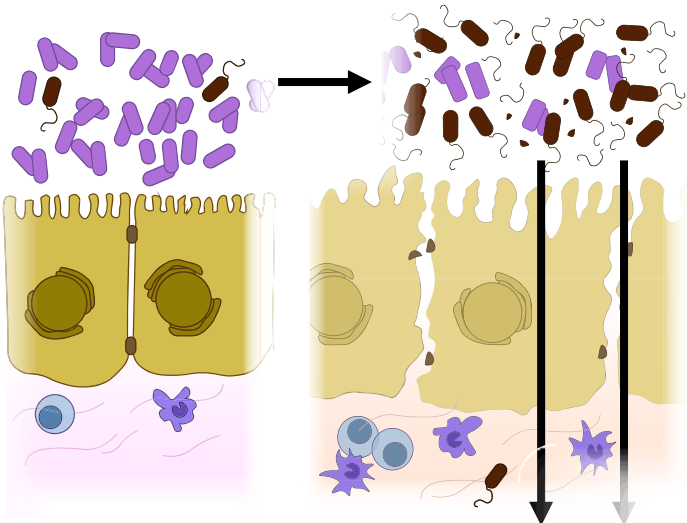
ACLF Pathogenesis: a still uncompleted history

Chapter 1: Inducers of inflammation

Normal mucose and microbiota

Lachnospiraceae and other spp.

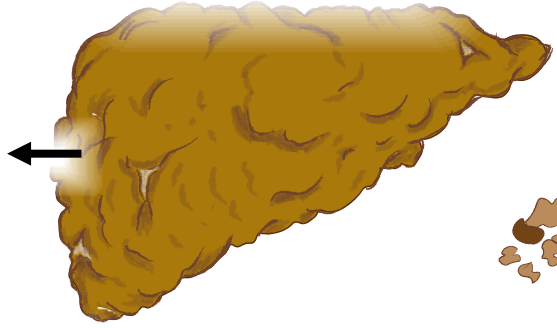
ENTEROBACTERIACEAE



CHANGES in GUT MICROBIOTA
Disbiosis and ↑LPS

CIRRHOSIS and PORTAL HYPERTENSION

INCREASED INTESTINAL PERMEABILITY

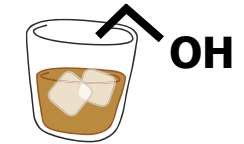


BACTERIAL TRANSLOCATION

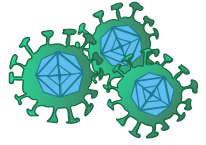
SBP

PAMPS

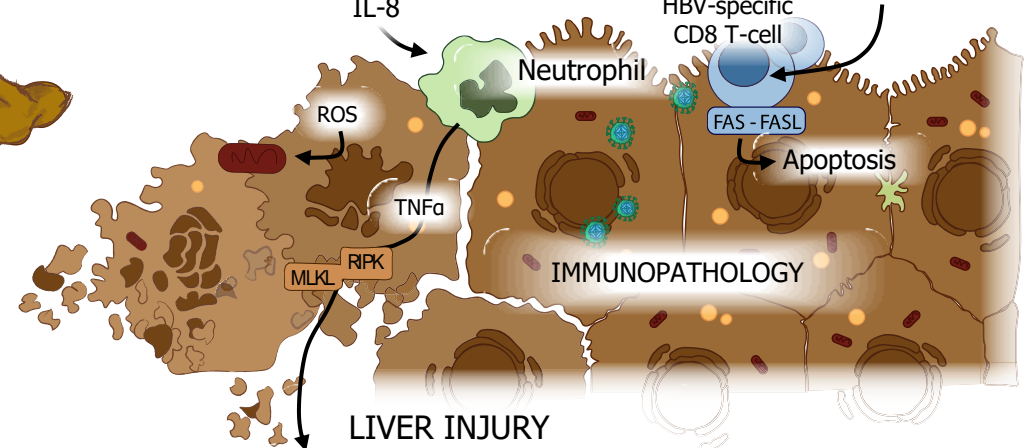
PATHOGEN ASSOCIATED MOLECULAR PATTERNS



ALCOHOLIC HEPATITIS



REACTIVATION of HBV



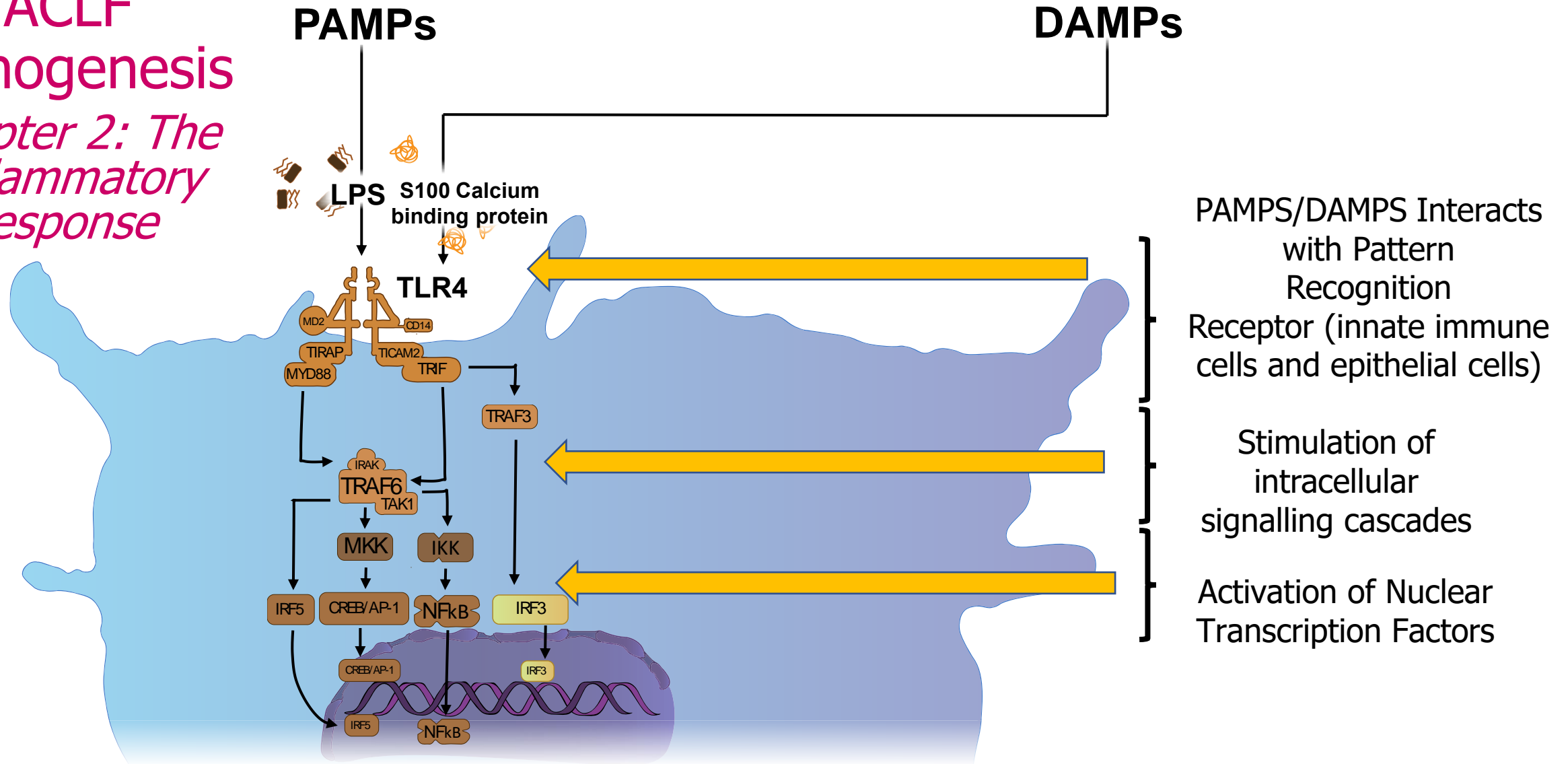
LIVER INJURY NECROSIS

DAMPs

DAMAGE ASSOCIATED MOLECULAR PATTERNS

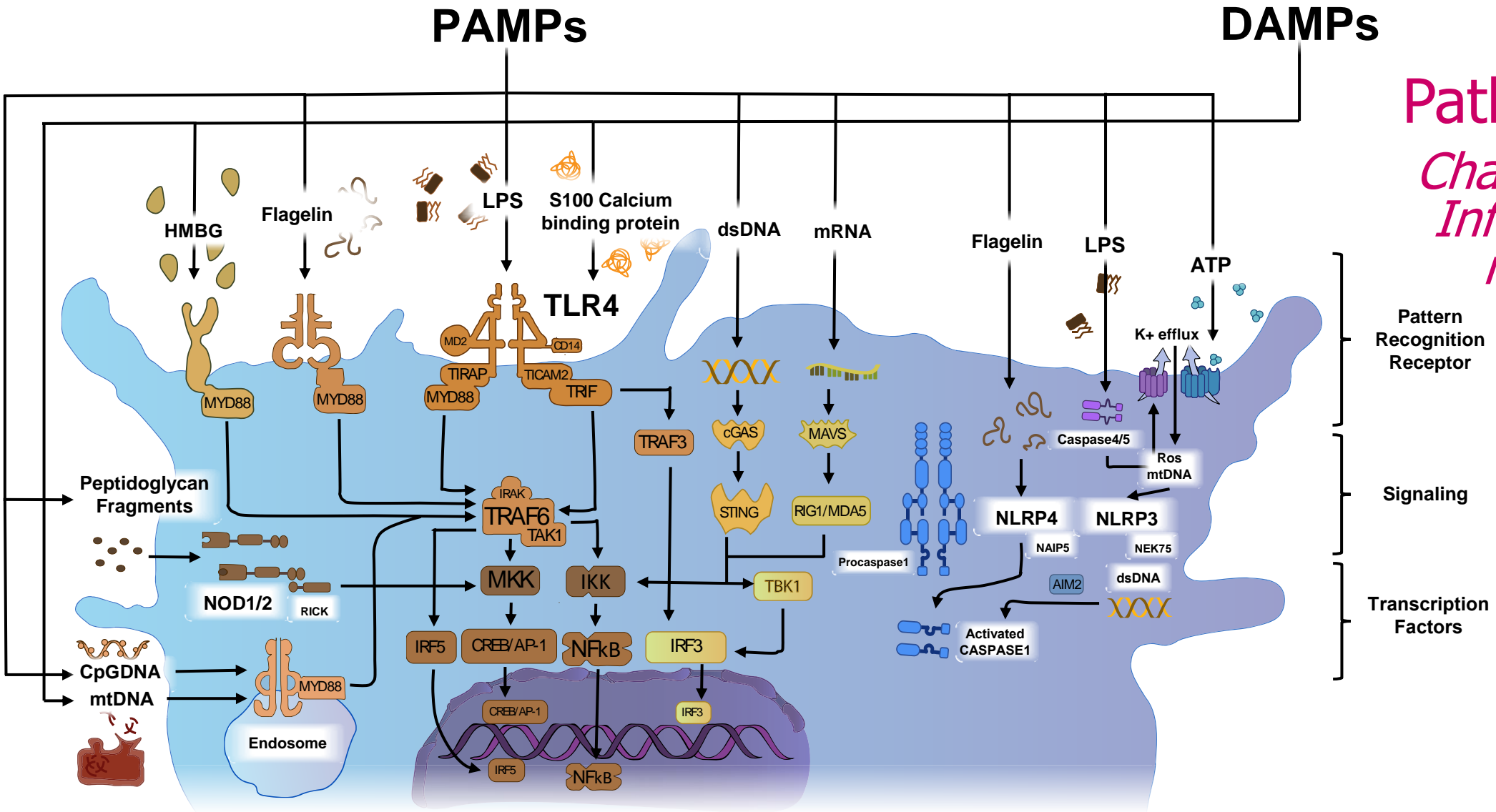
ACLF Pathogenesis

Chapter 2: The Inflammatory response



ACLF Pathogenesis

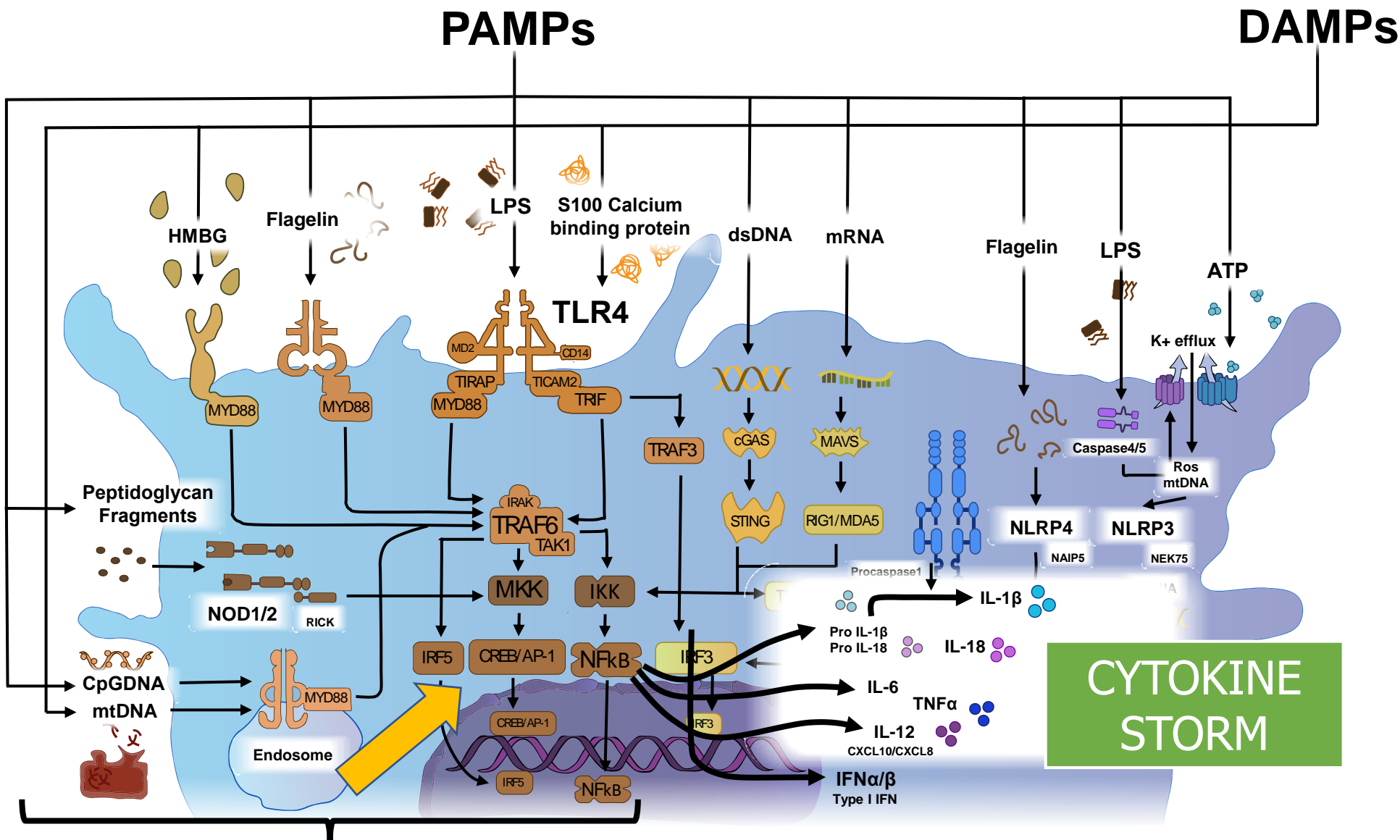
Chapter 2: The Inflammatory response



Different PAMPs and DAMPs interact with specific pattern recognition receptors and promote specific signalling and transcription process

ACLF Pathogenesis

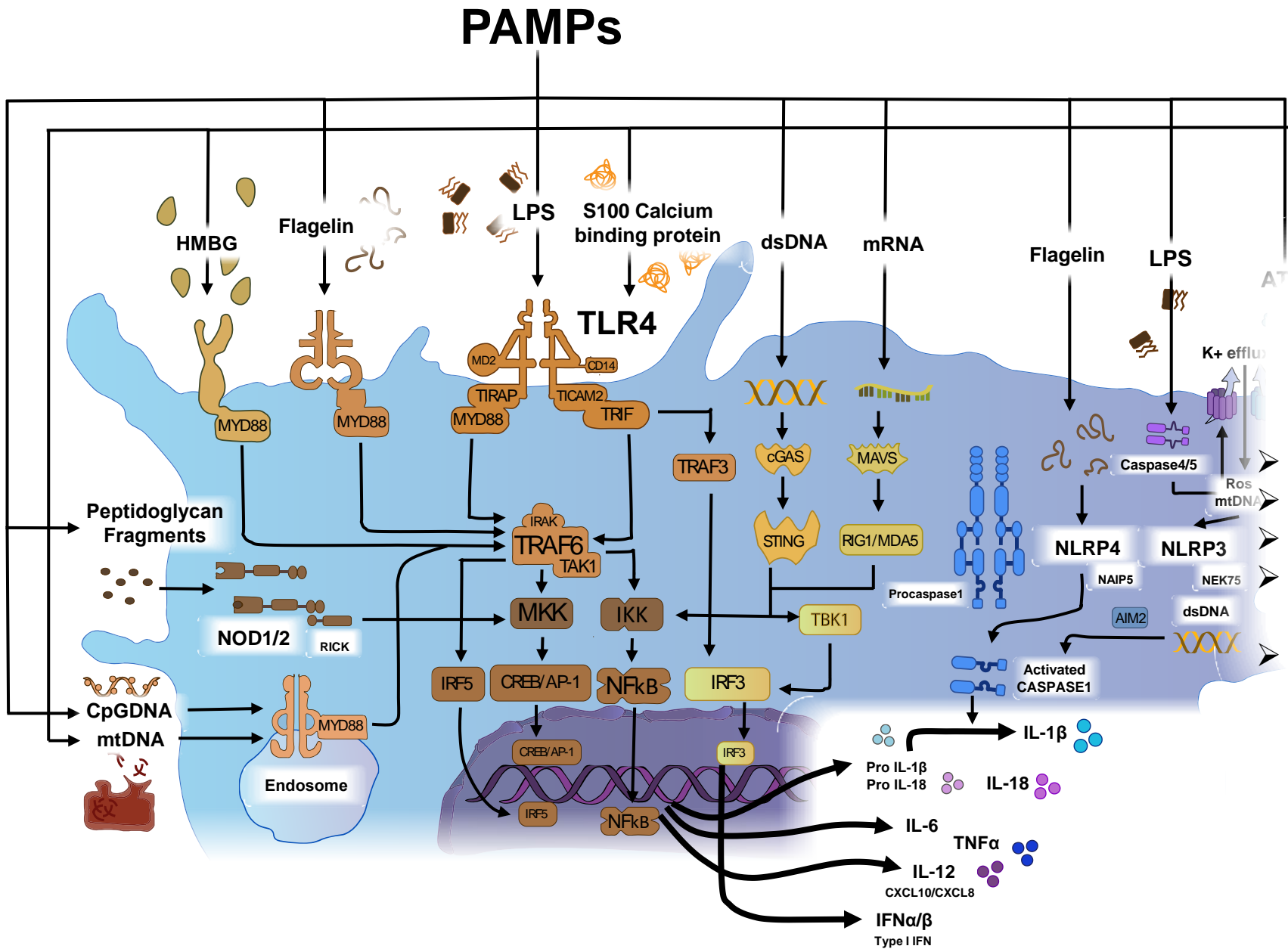
Chapter 2: The Inflammatory response



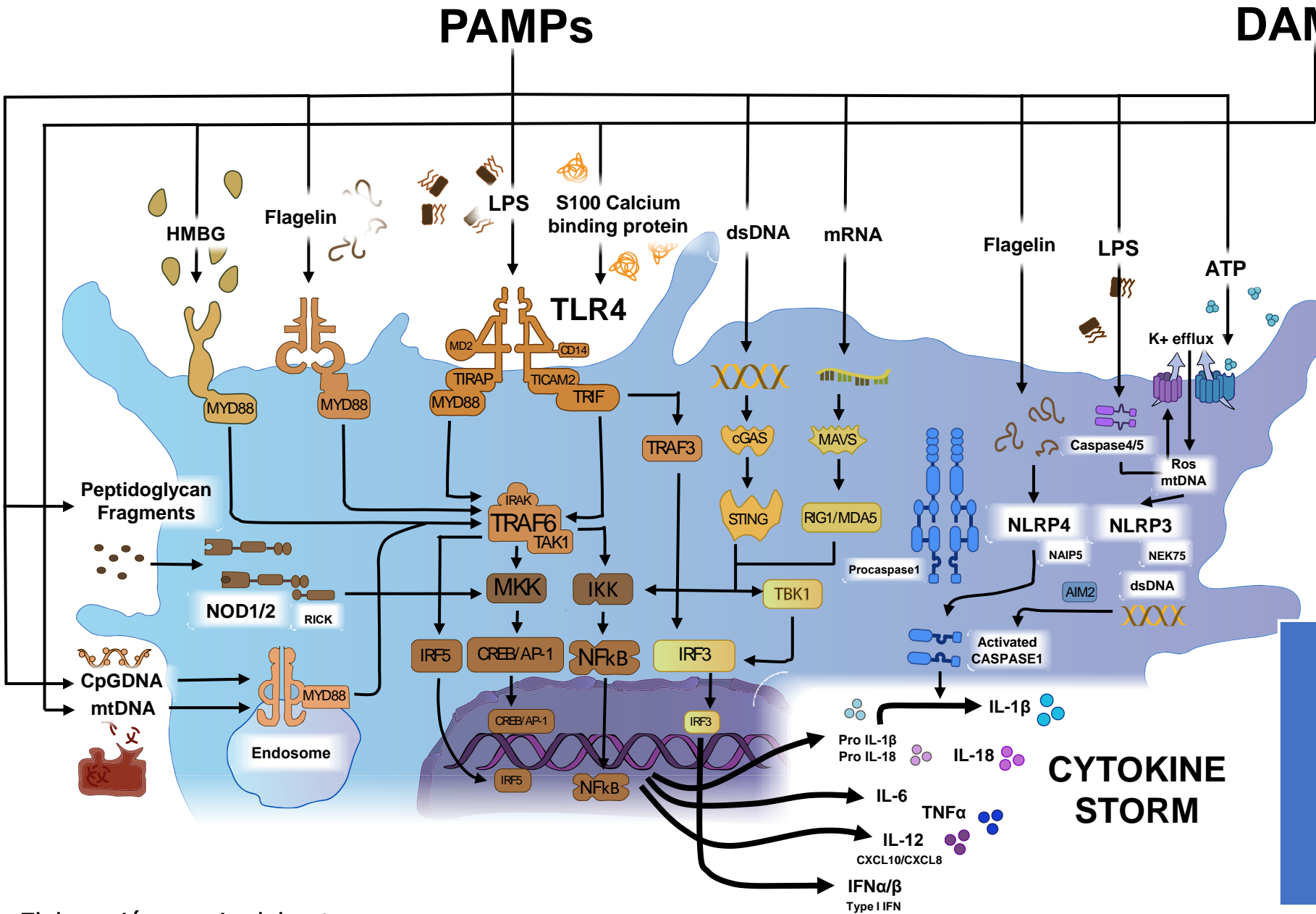
Induction of genes encoding molecules implicated in inflammation

ACLF Pathogenesis

Chapter 2: The Inflammatory response



- PROINFLAMMATORY RESPONSE**
- Cellular recruitment
 - Increased Cytokine Production
 - Endothelial Activation
 - Activation of TH1/TH17 Cells (Adaptive immunity)
 - Upregulation of Monocytes



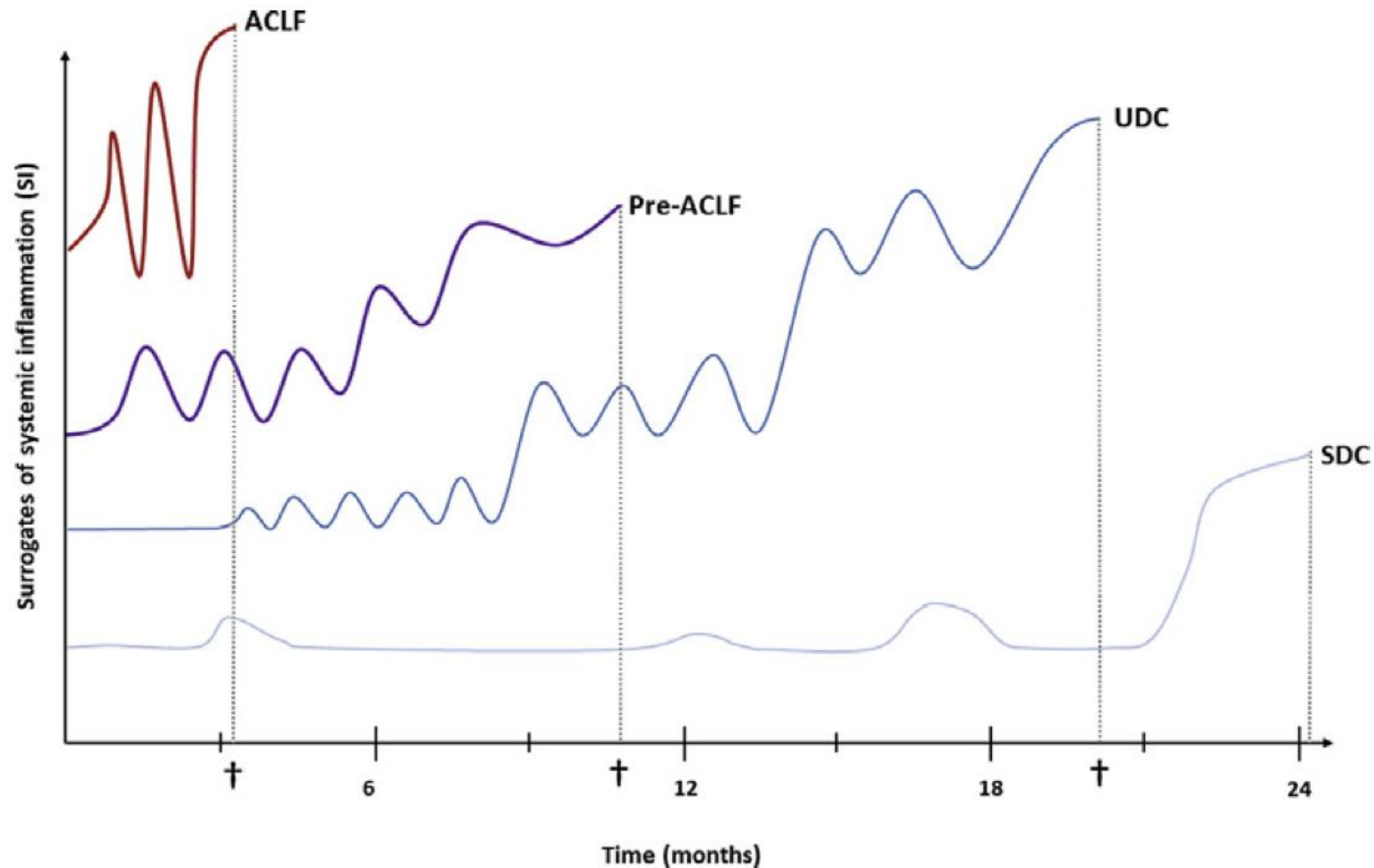
If the main objective of inflammatory response is:

TISSUE REPAIR
OR
INFECTION CONTROL

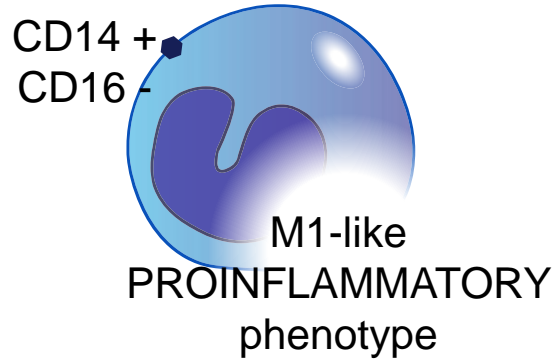


Why in ACLF there is FURTHER TISSUE DAMAGE and NO INFECTION CONTROL?

Patrón inflamatorio a lo largo del tiempo en los diferentes estadios de la cirrosis descompensada



MONOCYTE OF DECOMPENSATED CIRRHOTIC PATIENT



The monocytes of ACLF patients have a different transcriptomic profile

ACLF Pathogenesis

Chapter 3: Immunoexhaustion in ACLF monocytes

↑ **UPREGULATION** of anti-inflammatory markers

- Scavenger receptor CD163, MRC1...
- Growth factors
- Cytokines: **IL10**
- MERTK...

↓ **DOWNREGULATION** of Pro-inflammatory markers

- Cytokines: **TNF α** , IL23, **IL1 β** ...
- Chemokines: CCL4, CXCL9, CXCL10
- Co-stimulator in AP **CF80/CD83**
- STAT1...

DEFECTIVE ANTIBACTERIAL RESPONSE

↓ **ABILITY to DETECT BACTERIA**
↓TLR2 ↓TLR4

↓ **PHAGOCYTIC and OXIDATIVE CAPACITY**
↓IRF8 ↓PKKCE ↑Rnf145 (UbqE3)
NOX2complex – gp91phox

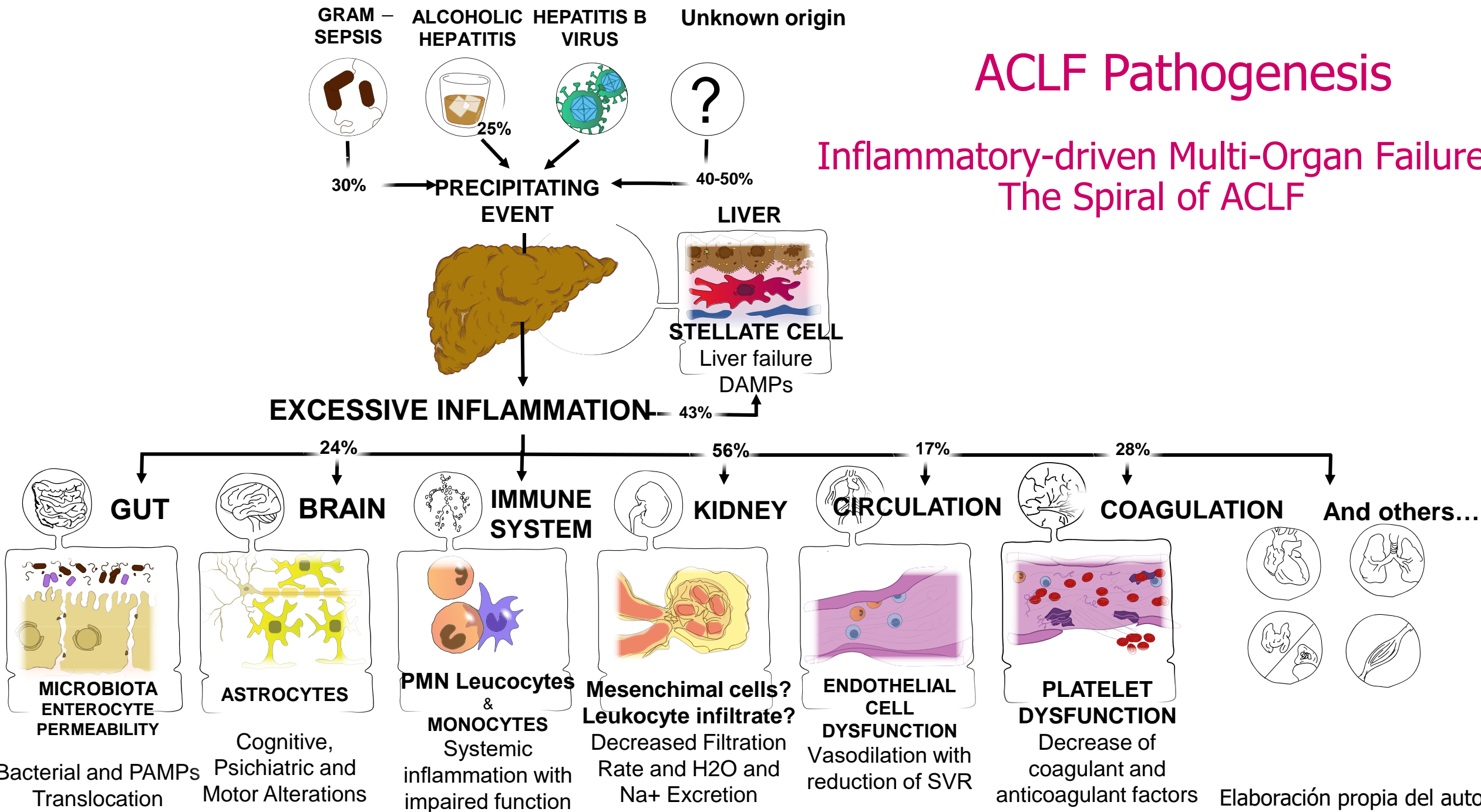
↓ **Antigen Presenting Cells related genes and T cell activation**
↓HLADR ↓CD80/CD83

M2-like ANTI-INFLAMMATORY PHENOTYPE
ACLF CHRONIC INFLAMMATION produces IMMUNE EXHAUSTION TOLERANCE and PARALYSIS

Korf et al. Gut 2018

ACLF Pathogenesis

Inflammatory-driven Multi-Organ Failure
The Spiral of ACLF



Sistema inmune



Inflamación

Incremento del consumo de energía del sistema inmune

Disfunción inmune
Infecciones secundarias

Sangre



Ácidos grasos

Eicosanoides

Sangre

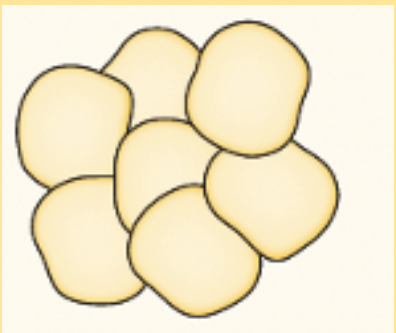


Hiperamoniemia

Aminoácidos

Tejido adiposo

Lipólisis



Hígado y otros órganos

Disfunción Mitocondrial

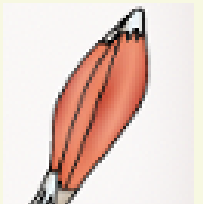
Alteración de OXPHOS

Glicolisis

Estrés oxidativo

MUERTE CELULAR

Músculo



Proteólisis

Intestino



Traslocación bacteriana
Disbiosis

La presentación habitual del paciente cirrótico avanzado

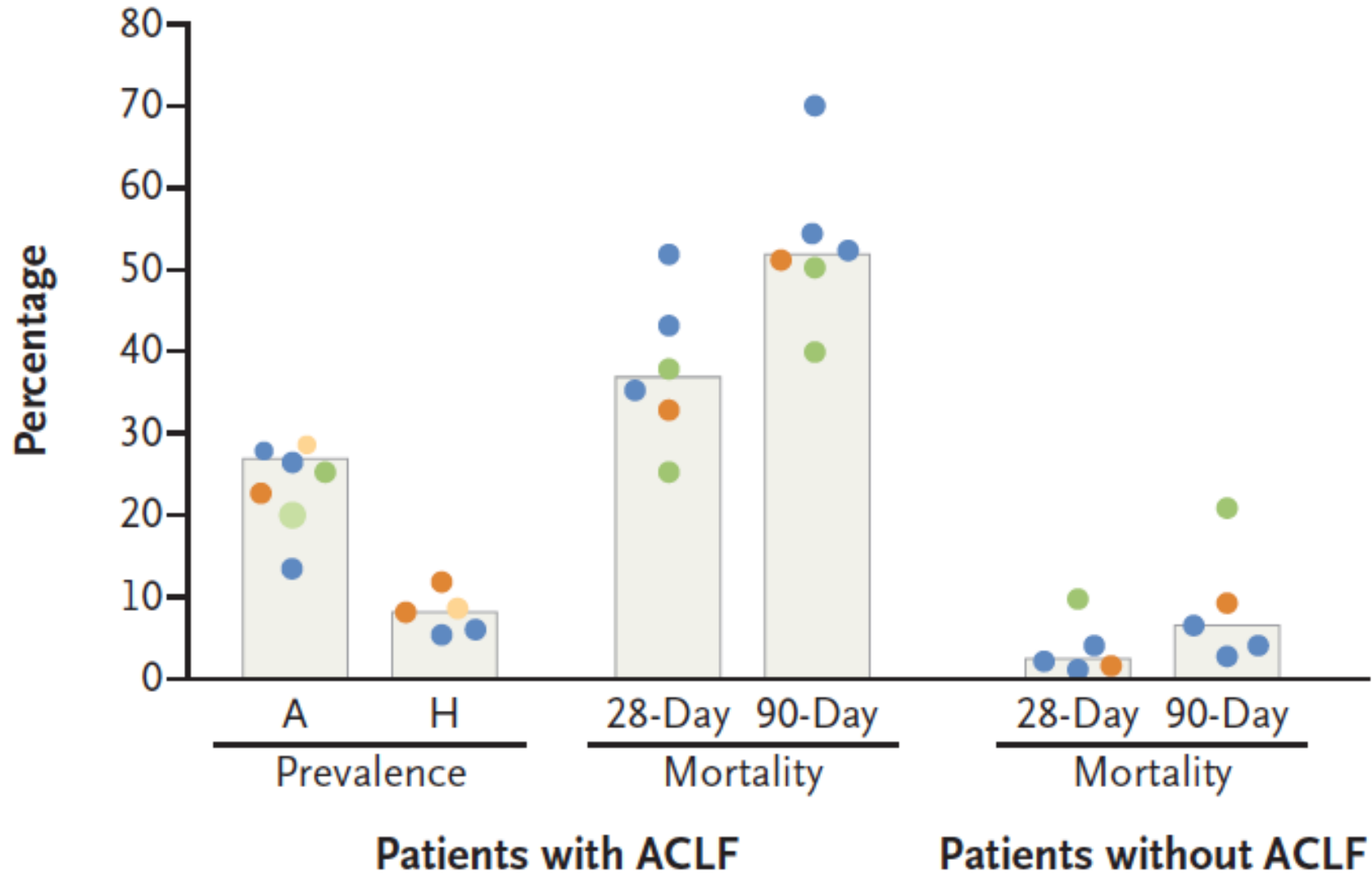


Diagnóstico del año 2000: Cirrosis descompensada
Diagnóstico del año 2021: ACLF

¿Son cosas distintas?

- El concepto de ACLF
- La patogenia
- La valoración del pronóstico

La indudable influencia pronóstica de ACLF



A practical stepwise approach to prognostic evaluation in ACLF

- **1st step:** Evaluate the presence of organ failure
- *2nd step: Calibrate the severity for each individual patient*
- *3rd step: ACLF is a dynamic syndrome*

To Evaluate the presence of organ failure

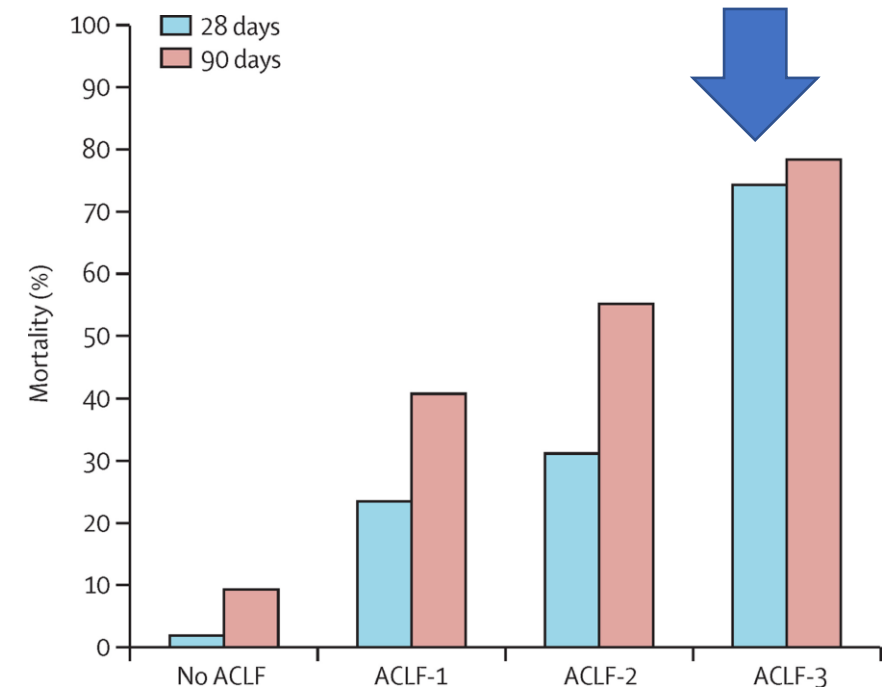
Organ System	1 Point	2 Points	3 Points
Liver	Bilirubin <6 mg/dl	Bilirubin 6.0–11.9 mg/dl	Bilirubin ≥12 mg/dl
Kidney	Creatinine <1.5 mg/dl Creatinine 1.5–1.9 mg/dl	Creatinine 2.0–3.4 mg/dl	Creatinine ≥3.5 mg/dl or RRT
Brain (West Haven criteria)	Grade 0	Grade 1–2	Grade 3–4
Coagulation	INR <2.0	INR 2.0–2.4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

Diagnosis and grading of ACLF

Based on results of the CANONIC study

ACLF identifies patients admitted to hospital with a complication of cirrhosis and with a 28-day mortality greater than 15%.

Patient Group	Prevalence % of patients	28-Day Mortality	Assigned Grade
Absence of OF	68.3	4.4	Absence of ACLF
Single, nonkidney OF without KD or BD	9.9	6.3	
Single KF	6.7	18.6	ACLF-1
Single, nonkidney 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



The American perspective

Two or more from

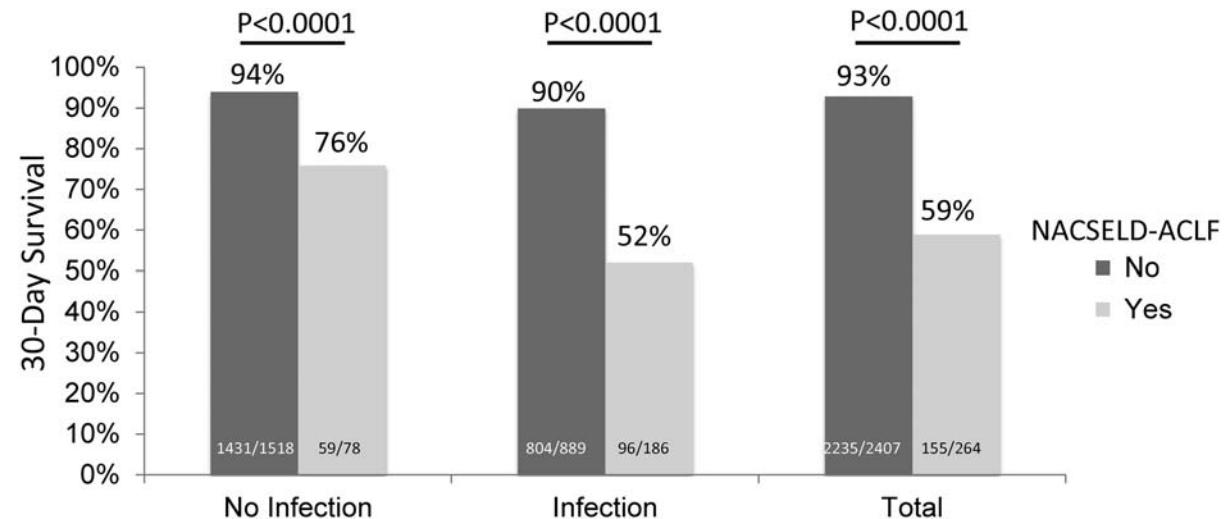
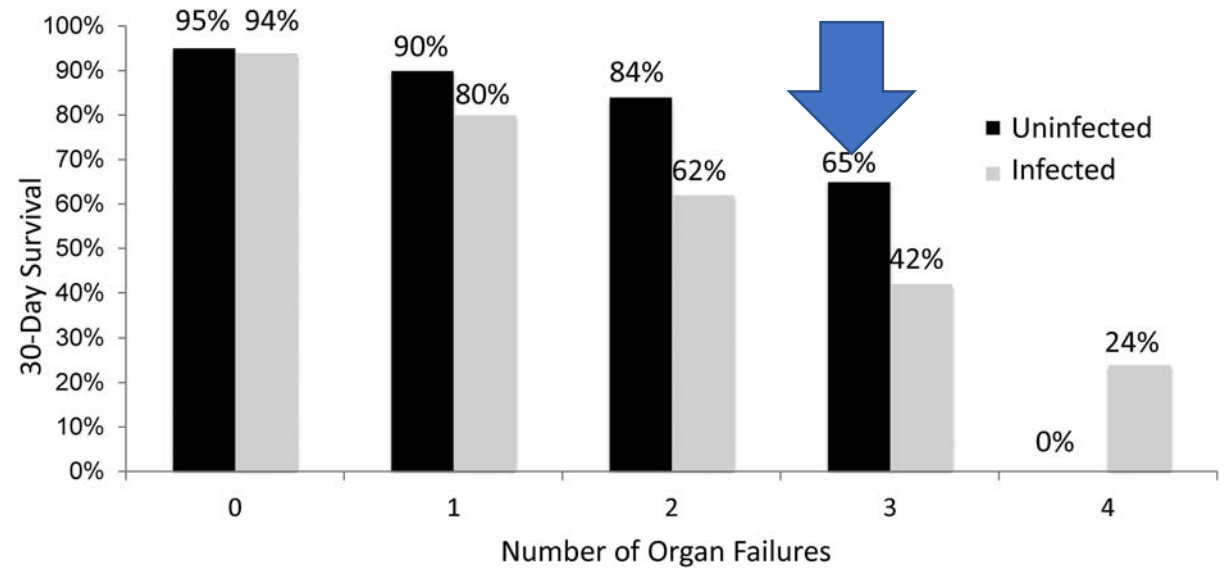
A) Kidney: need for RRT.

B) Brain: HE grade 3-4 according to West-Haven criteria.

C) Circulation: shock defined by MAP <60 mmHg or a reduction of 40 mmHg in systolic blood pressure from baseline, despite adequate fluid resuscitation

D) Respiratory: need for bilevel positive airway pressure or mechanical ventilation

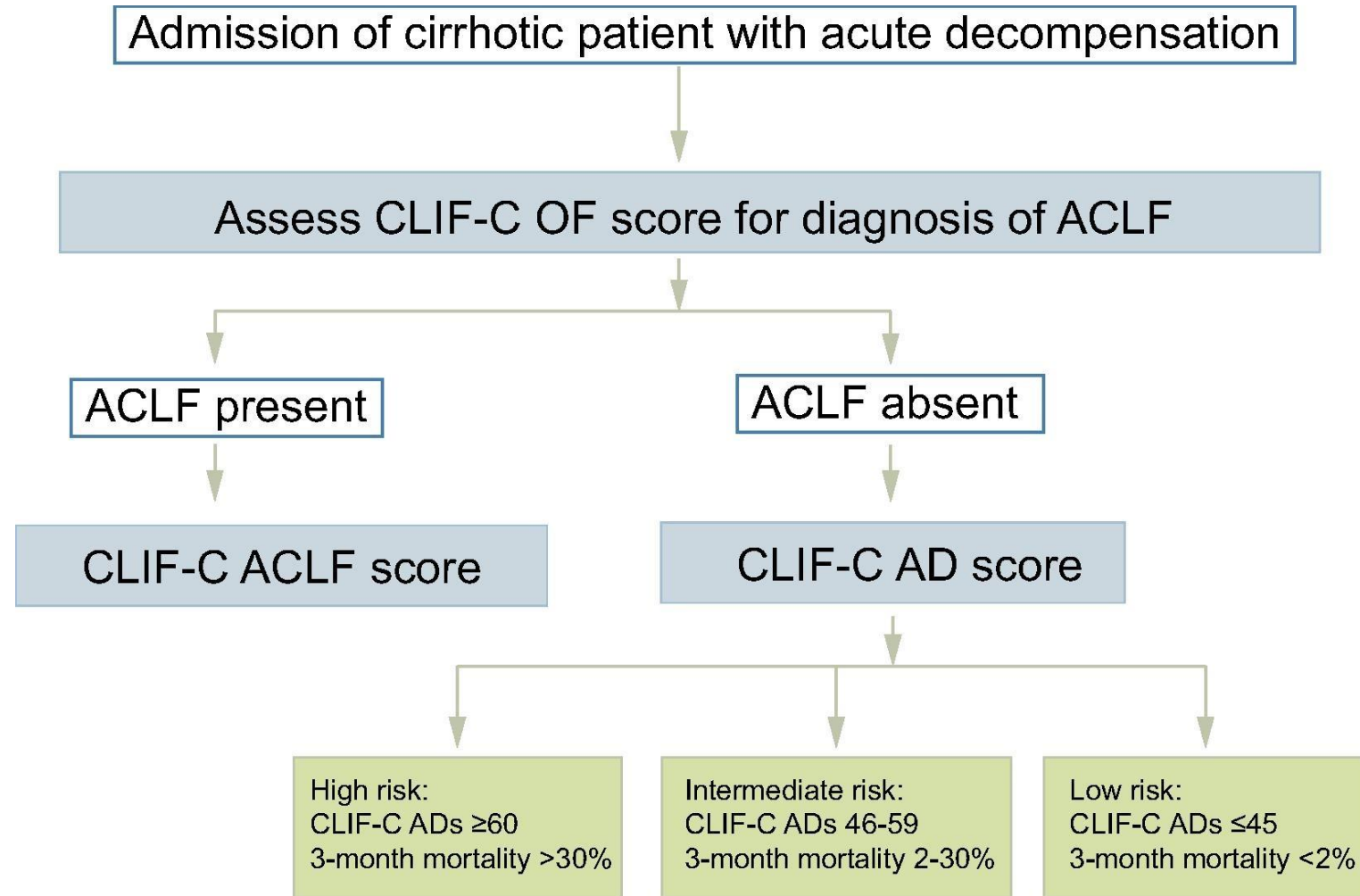
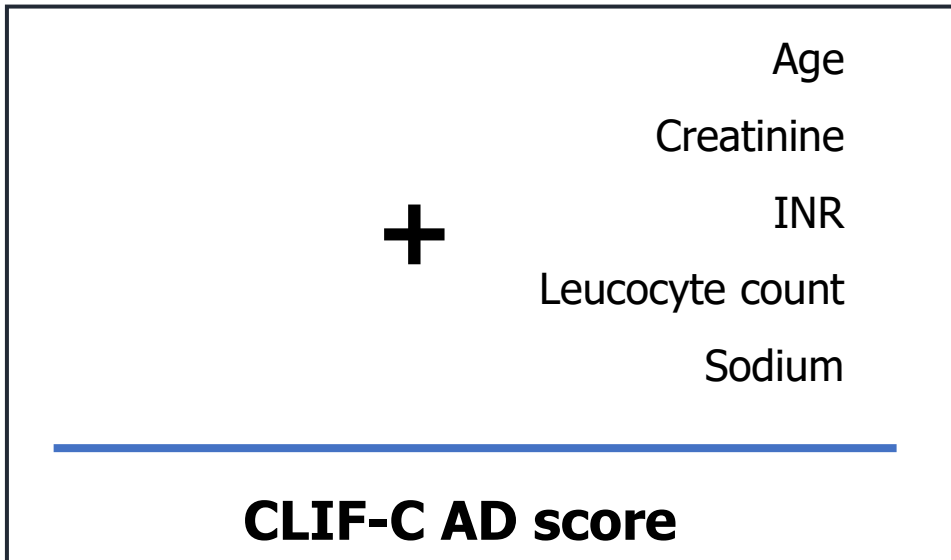
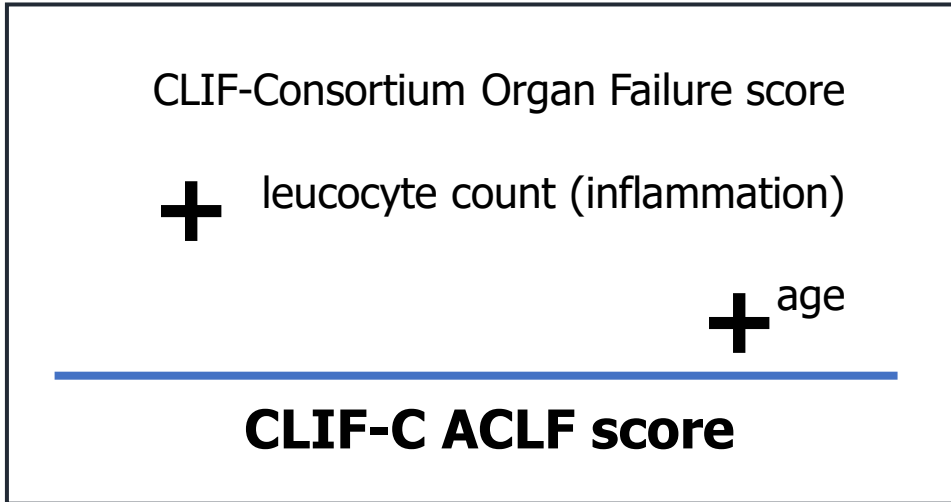
O'Leary JG et al Hepatology 2018



A practical stepwise approach to prognostic evaluation in ACLF

- 1st step: Evaluate the presence of organ failure
- 2nd step: Calibrate the severity for each individual patient
- 3rd step: *ACLF is a dynamic syndrome*

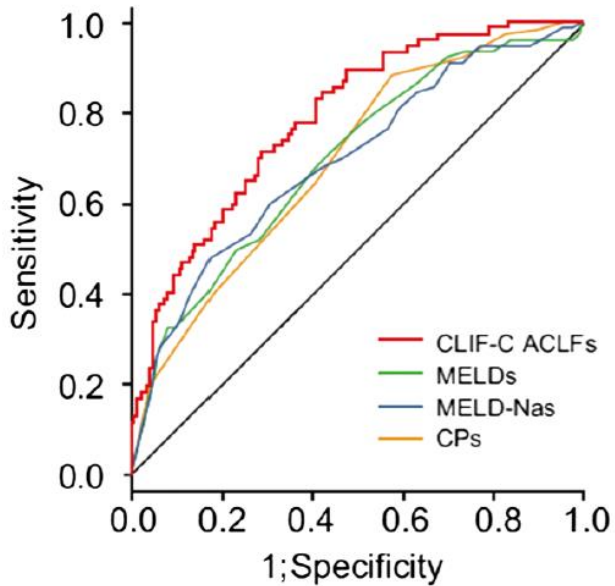
Prediction of prognosis in ACLF



<http://www.efclif.com/>

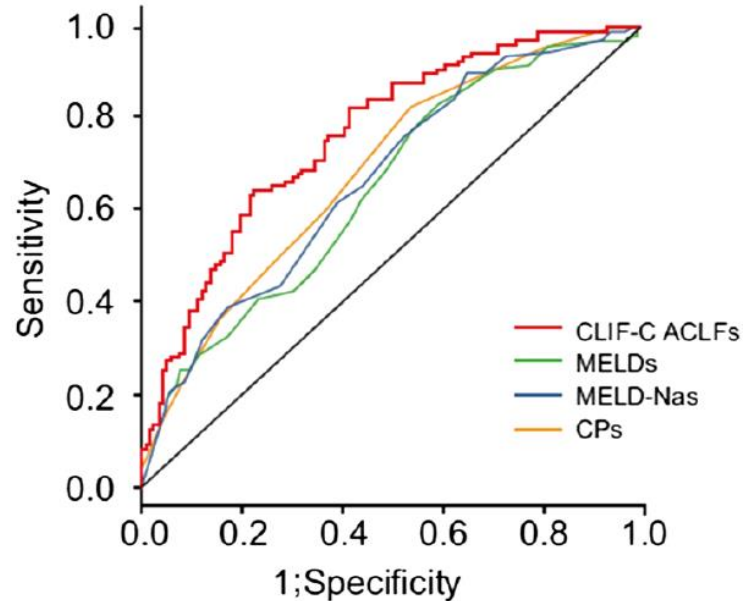
Accuracy of CLIF-C ACLF score

A Prediction of 28-day mortality



	AUROC (95% CI)	<i>p</i> value; vs; CLIF-C ACLF
CLIF-C ACLFs	0.79 (0.73–0.85)	
MELDs	0.70 (0.62–0.77)	0.0089
MELD-Nas	0.70 (0.62–0.77)	0.0097
CPs	0.70 (0.63–0.77)	0.0075

B Prediction of 90-day mortality



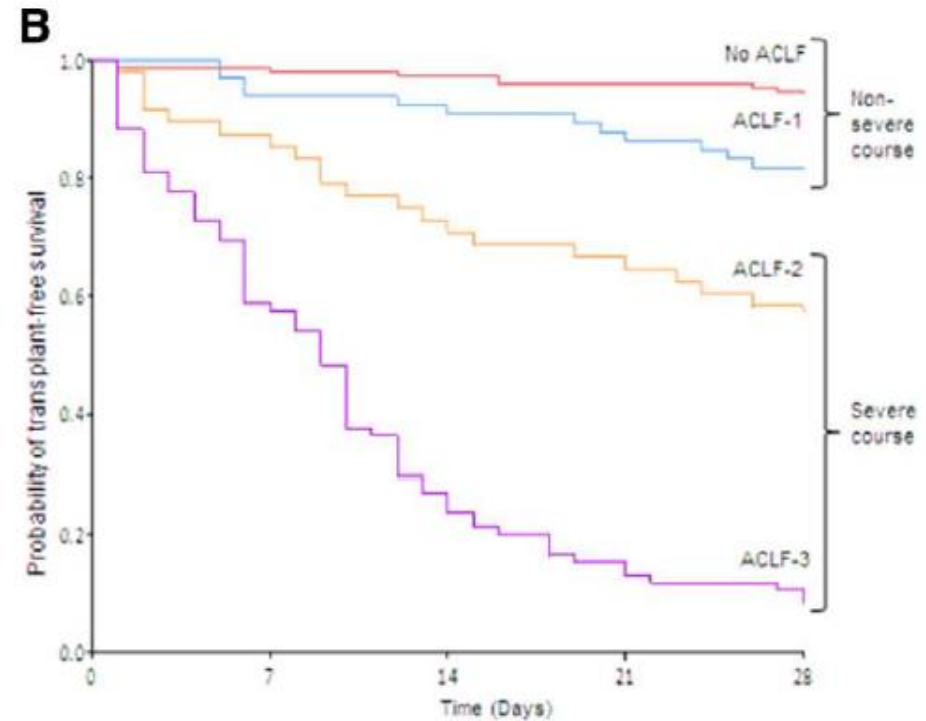
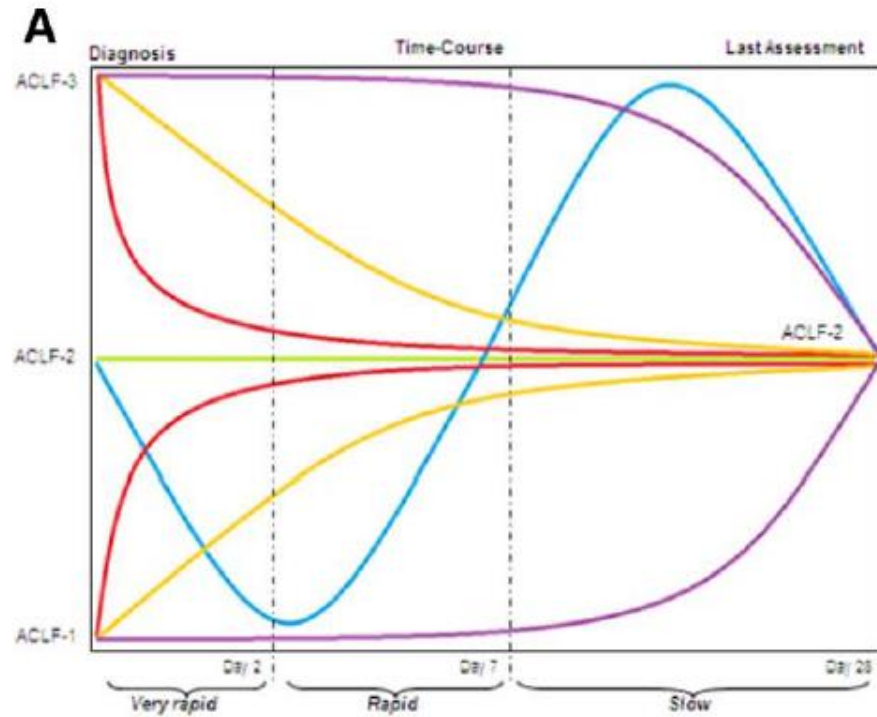
	AUROC (95% CI)	<i>p</i> value; vs; CLIF-C ACLF
CLIF-C ACLFs	0.76 (0.70–0.83)	
MELDs	0.65 (0.58–0.72)	0.0014
MELD-Nas	0.67 (0.60–0.74)	0.0082
CPs	0.69 (0.62–0.75)	0.0301

As compared with MELD, MELD-Na and Child-Pugh scores the AUROCs estimated for the CLIF-C ACLF score to predict 28-day and 90-day mortality were significantly higher

A practical stepwise approach to prognostic evaluation in ACLF

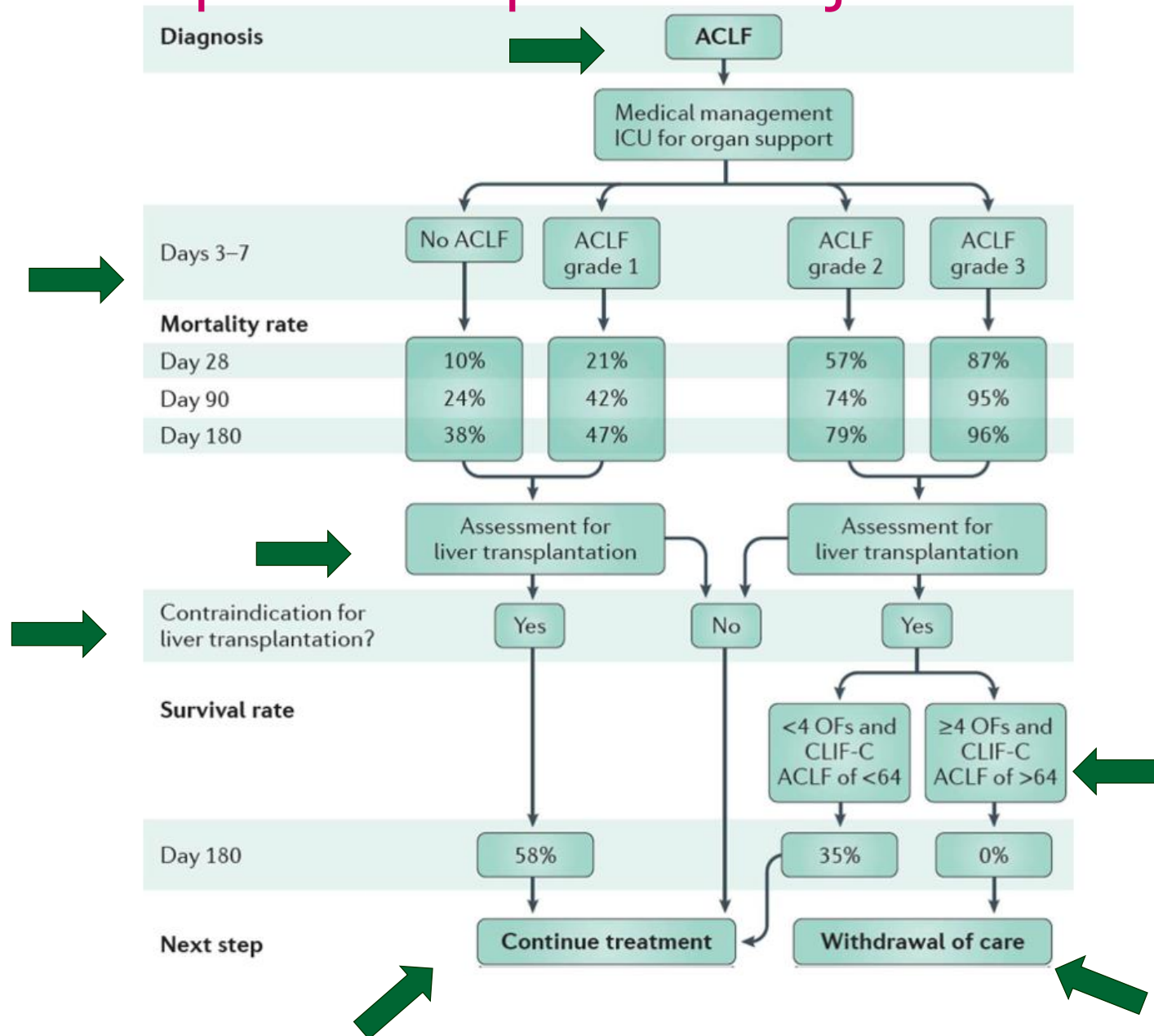
- 1st step: Evaluate the presence of organ failure
- 2nd step: Calibrate the severity for each individual patient
- 3rd step: ACLF is a dynamic syndrome

ACLF is a very dynamic syndrome



ACLF may resolve, improve, or worsen within a time-frame ranging from 1-2 days to 2-4 weeks. Prognosis correlates better with clinical course than with ACLF grade at diagnosis. ACLF is a dynamic process, but outcome can be predicted at day 7.

La calibración del pronóstico permite mejorar la toma de decisiones

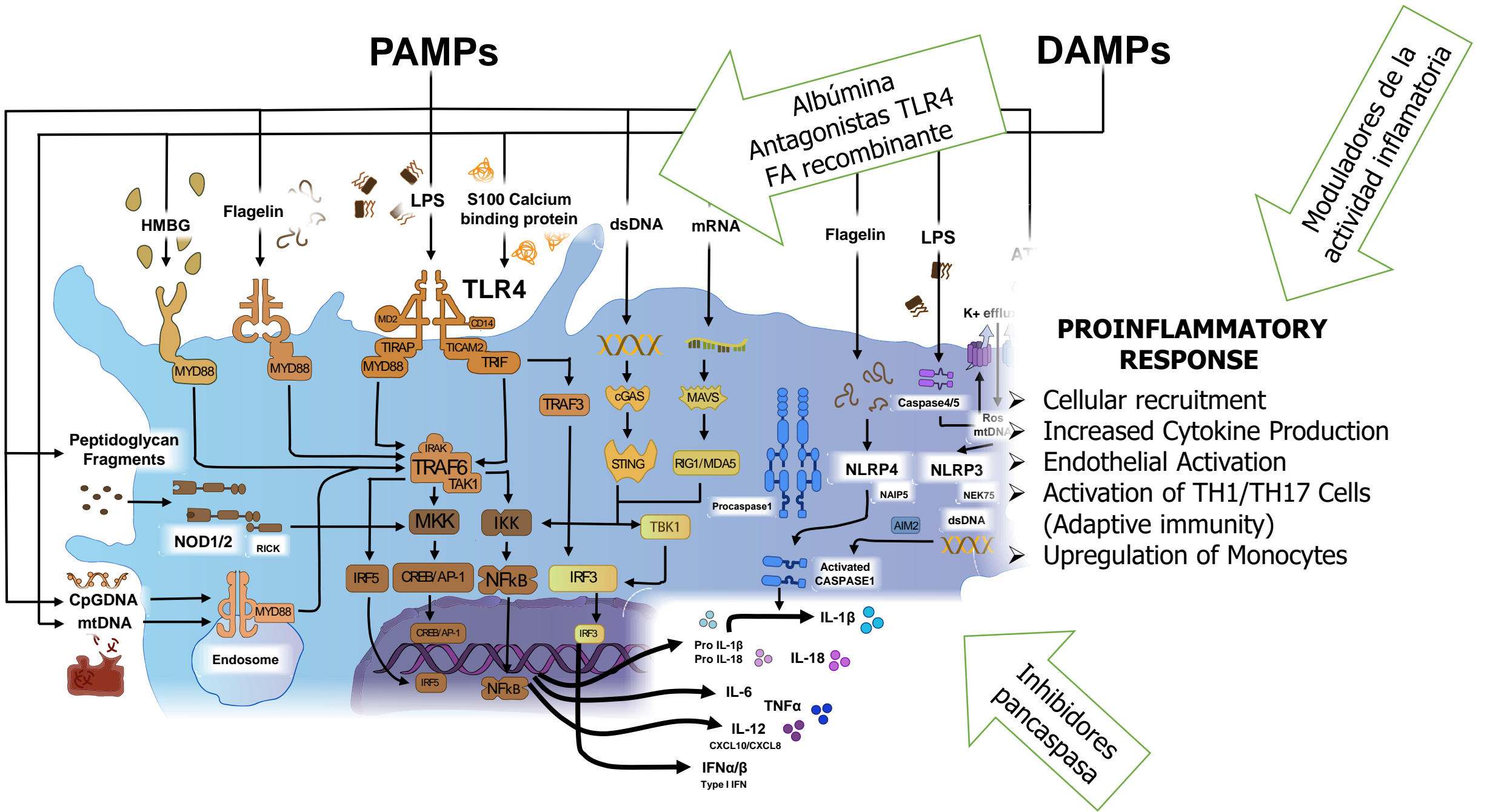


Requirements of future prognostic assessment in ACLF

- Useful in the selection of specific therapies
- Determine when ICU care is appropriate or futile
- Should help to recognize which patients will benefit the most from regenerative therapy or liver support devices
- Improve selection of patients for early liver transplantation

From pathogenesis to prognosis and therapy

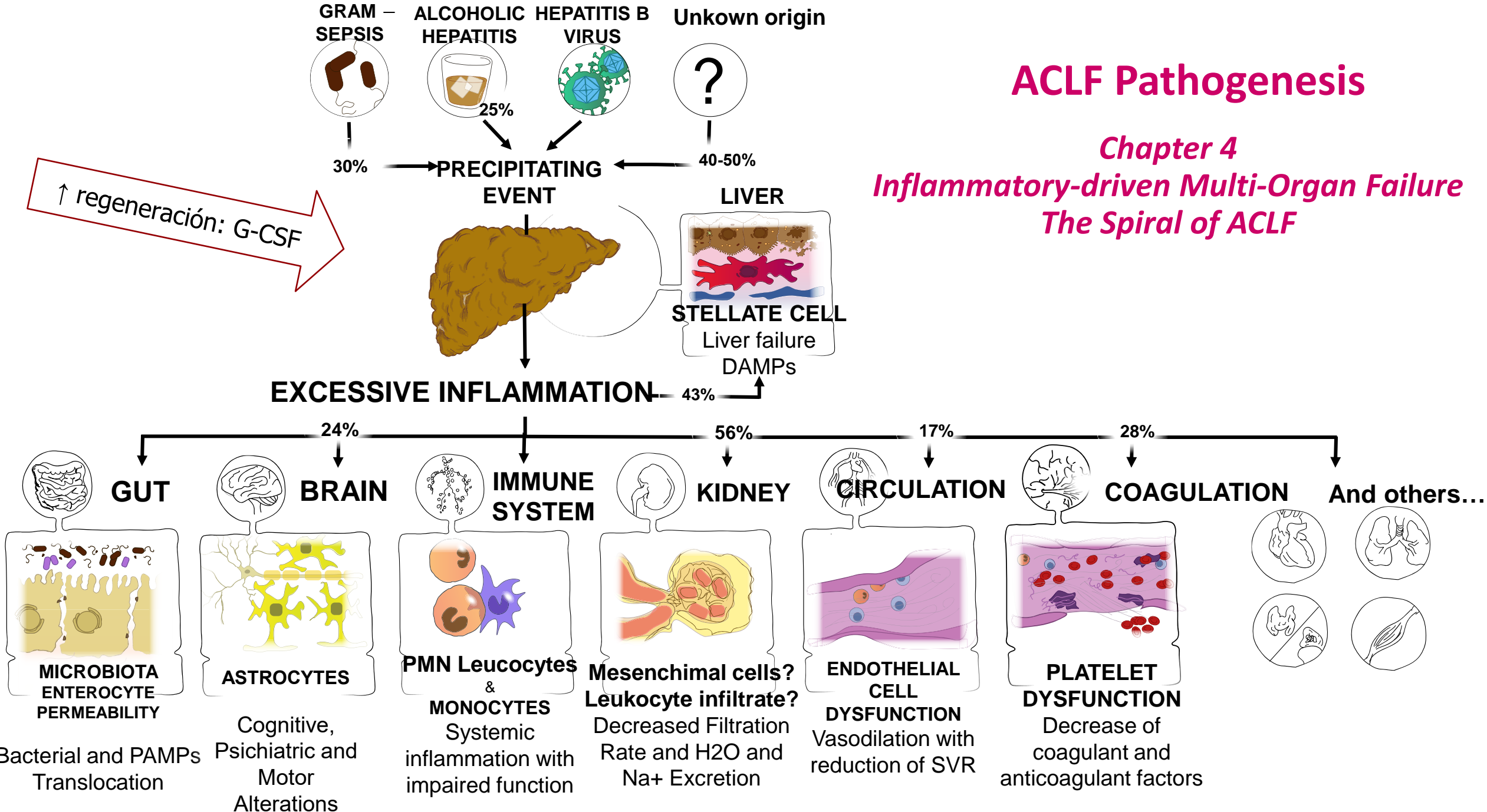
Pathogenetic findings	Potential prognostic implications	Consideration in current scores
Excessive DAMPs and PAMPs production	Potential use as future diagnostic biomarkers	No
Excessive inflammatory response	Relationship between severity of inflammation and prognosis	Yes (leucocyte count are part of CLIF-ACLF scores. CRP is associated to prognosis)
Altered inflammatory response	Inflammatory/genetic signatures with prognostic implications	No
Immunoexhaustion	Characterization of circulating immune-suppressed cells in patients with ACLF	No
Extension of inflammation to other organs	Organ failure	Yes Organ failure is essential in prognostic evaluation (EASL-CLIF/AASLD-NACSLD)

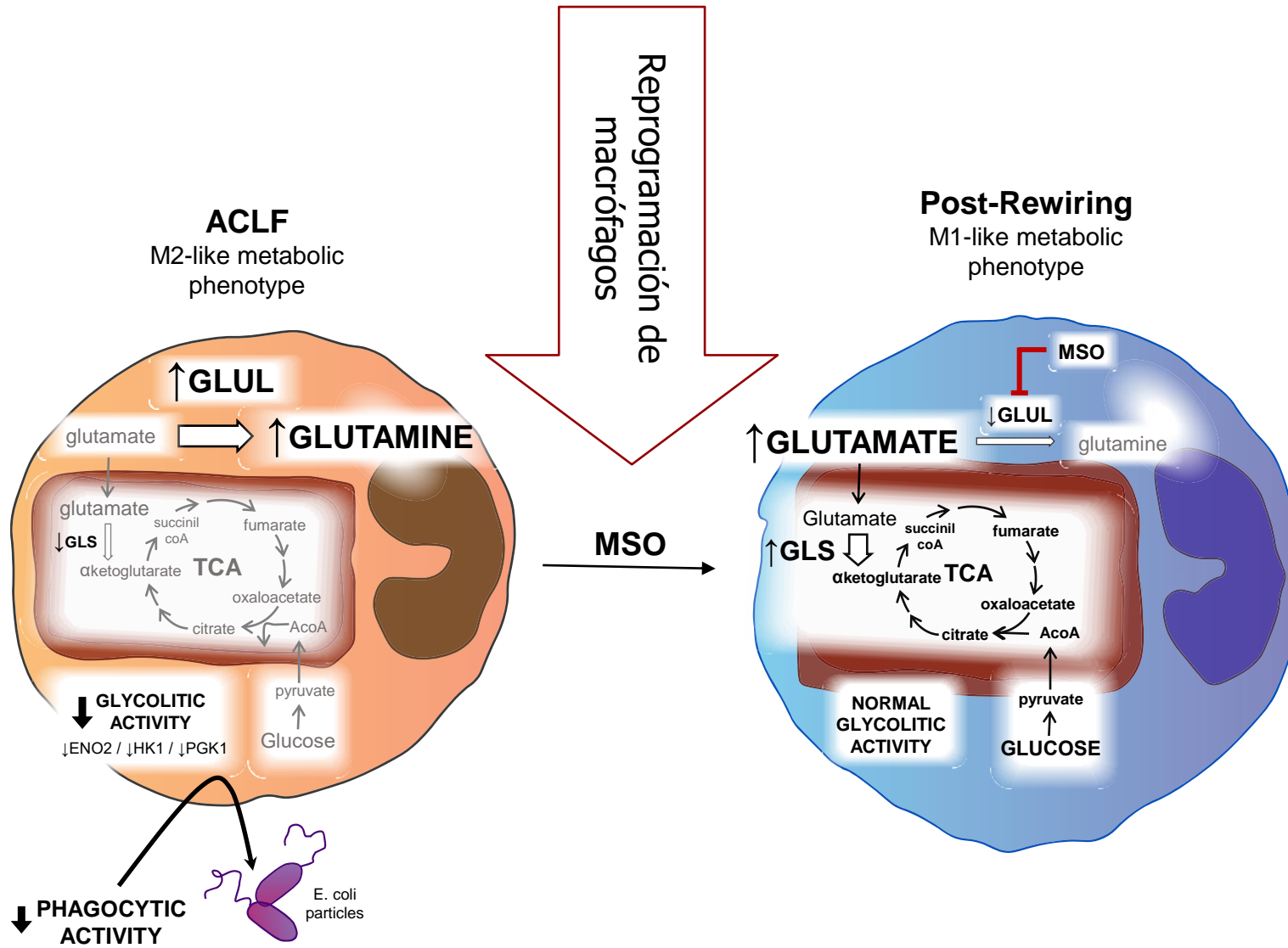


ACLF Pathogenesis

Chapter 4

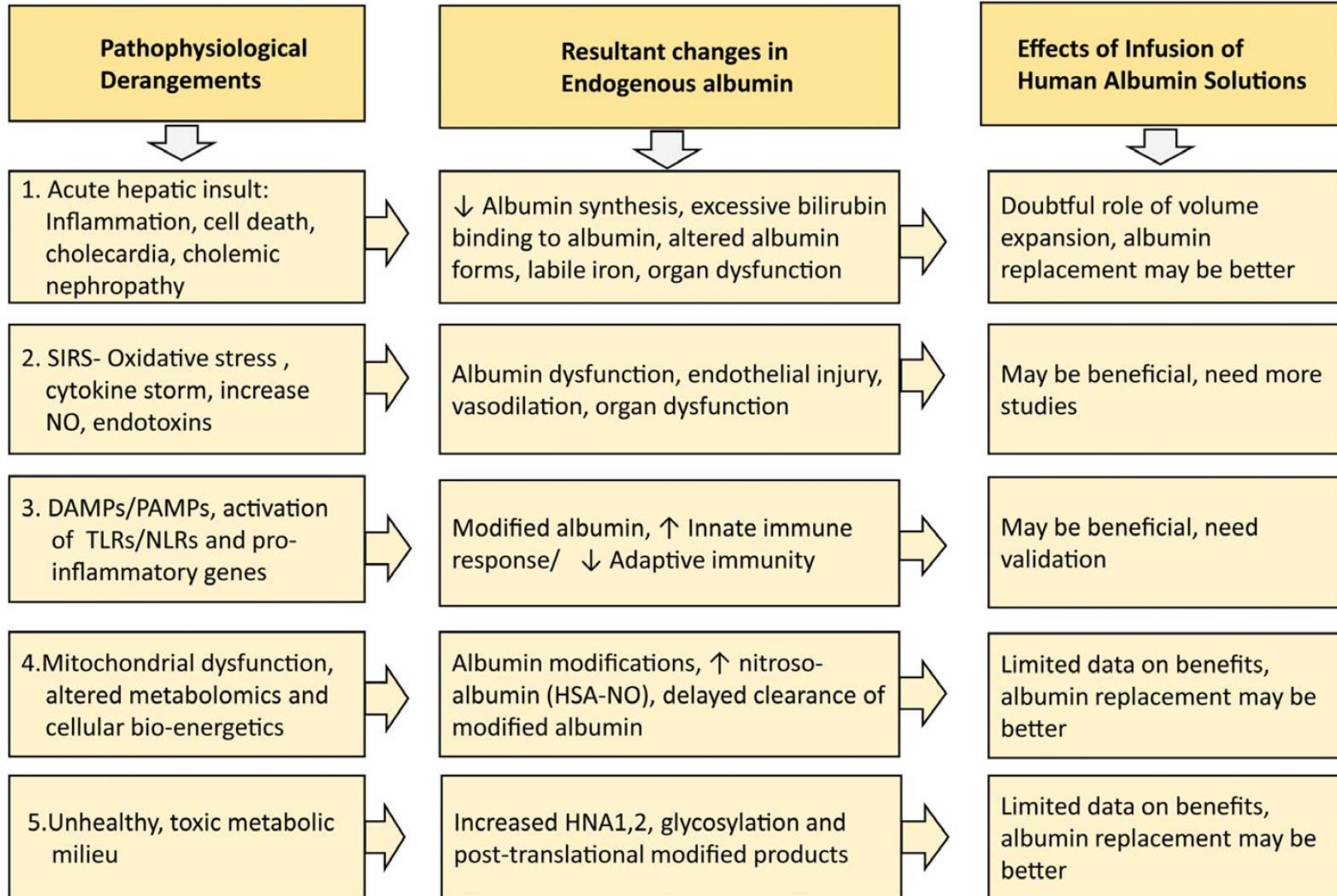
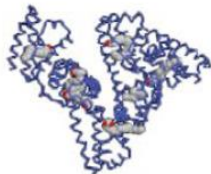
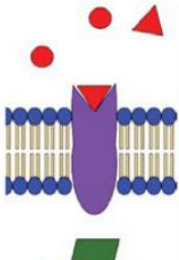
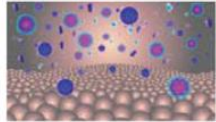
Inflammatory-driven Multi-Organ Failure The Spiral of ACLF





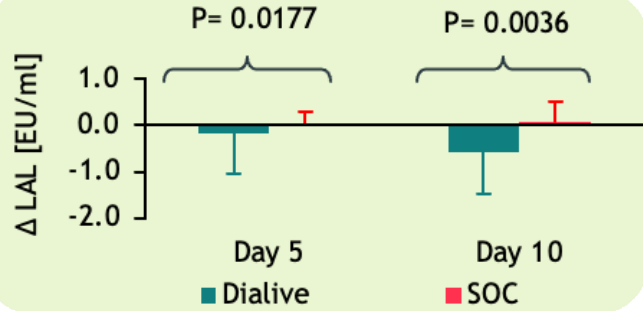
También la albúmina (a lo mejor)

ACLF

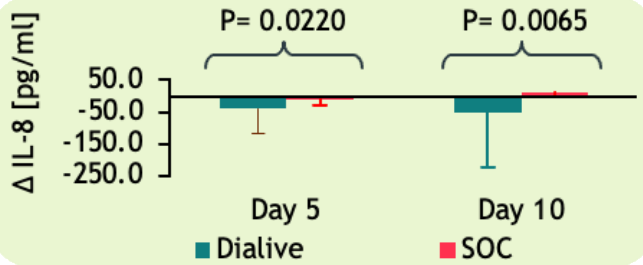


DIALIVE modifies pathophysiological process involved in the pathogenesis of ACLF⁽¹⁾

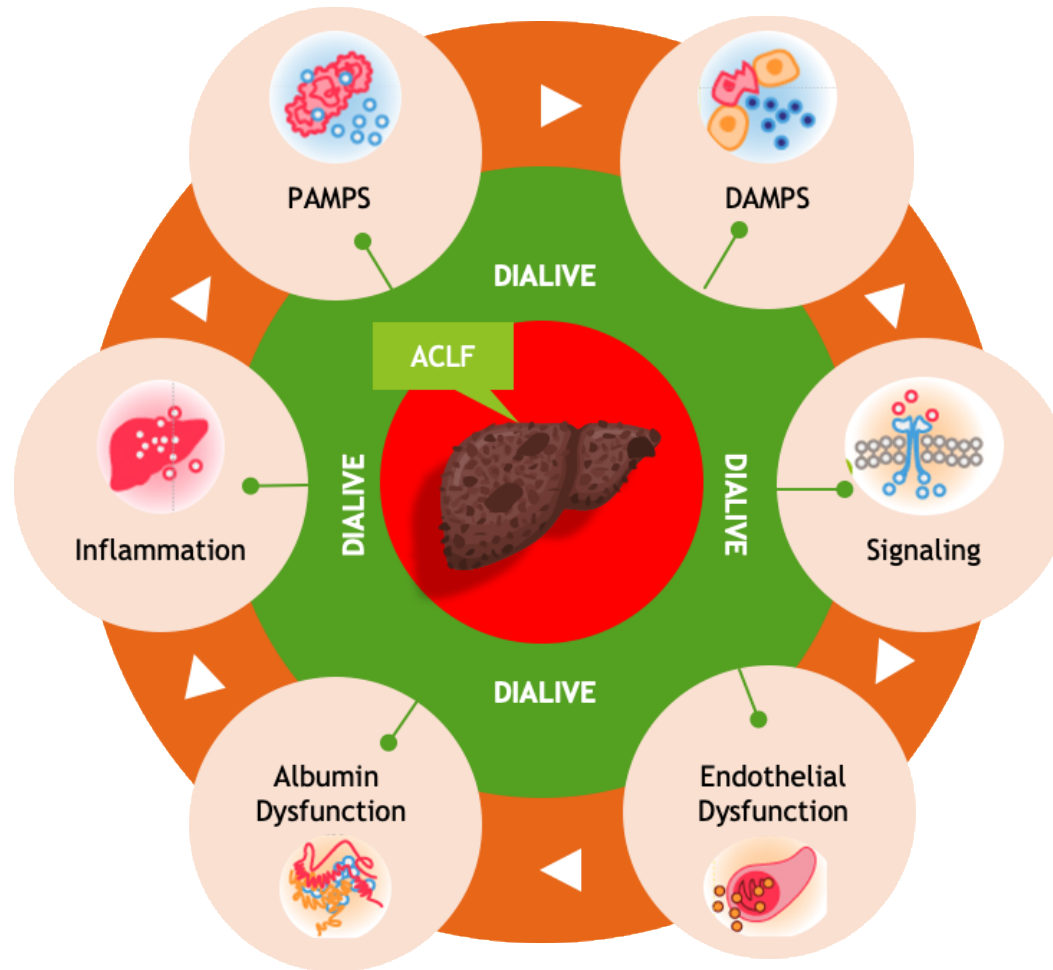
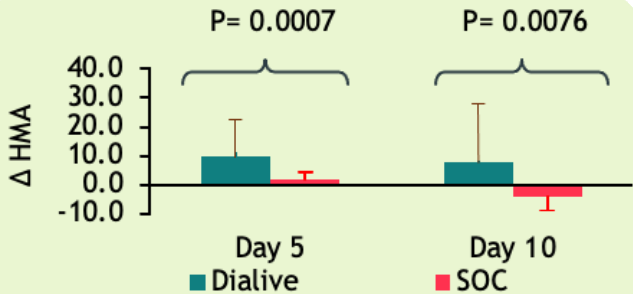
PAMPS



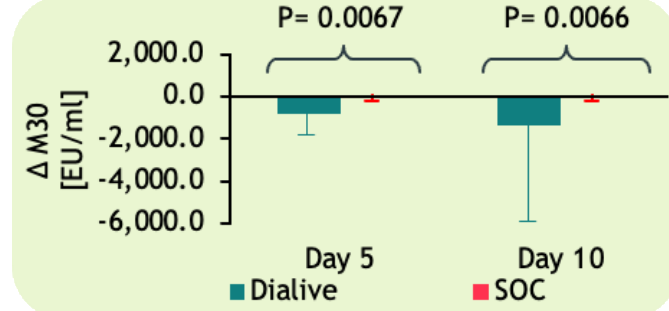
Systemic Inflammation and immune dysfunction



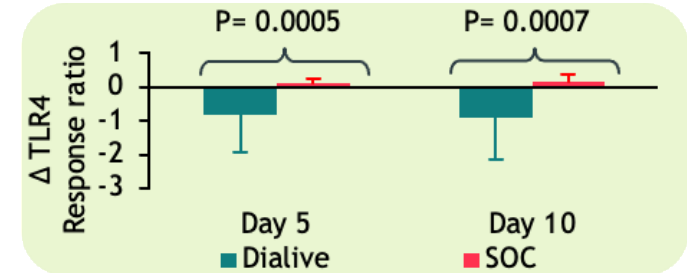
Albumin dysfunction



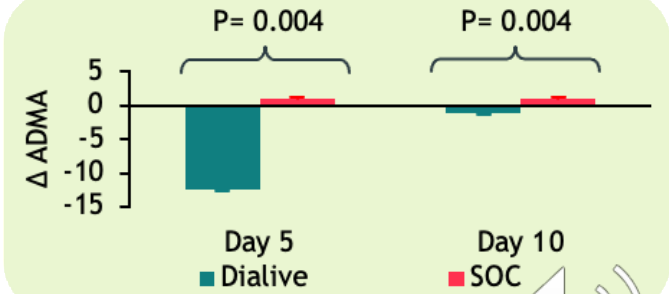
DAMPS



Increased cellular signaling through TLR4 / inflammasome

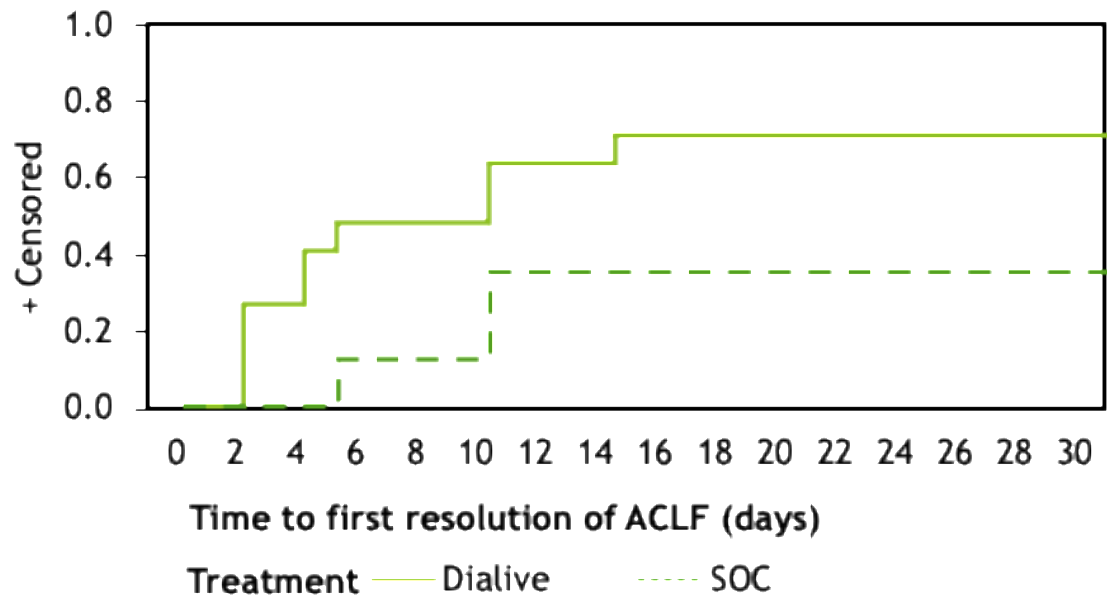


Endothelial dysfunction



DIALIVE modifies outcomes in patients with ACLF

SURVIVAL CURVES FOR TIME TO RESOLUTION OF ACLF



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



Conclusiones

- El fracaso hepático agudo sobre crónico es un síndrome caracterizado por una patogenia específica asociada a la exacerbación de la respuesta inflamatoria.
- El fracaso hepático agudo sobre crónico se asocia a una elevada mortalidad a corto y medio plazo.
- La presencia de fracaso de órganos y el número de órganos que fracasan determinan el pronóstico el cual debe evaluarse de forma dinámica en los primeros 3-7 días desde el diagnóstico.
- El mejor conocimiento de la patogenia puede permitir en el futuro determinar marcadores específicos del pronóstico así como dianas terapéuticas más precisas.



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