

“Acute-on-chronic liver failure”: prognosis and treatment

J. Fernández,

Liver ICU, Hospital Clinic of Barcelona, Spain

ACD, Barcelona January 14 2016

CLINICAL COURSE OF CIRRHOSIS: PHASES

1. **Compensated cirrhosis (CC).** Slow (>10-15y) progression of fibrosis and portal hypertension
2. **Acute decompensation (AD):** 70% of patients admitted to hospital with cirrhosis. Acute development of ascites, gastrointestinal hemorrhage, hepatic encephalopathy and/or acute bacterial infection (**mean survival <3 y**)
3. **Acute-on-Chronic Liver Failure (ACLF):** 32% of patients admitted to hospital (22% present ACLF at admission; 10% during hospitalization). **Characteristics:**
a). **AD**; b). **Organ failure(s)** (Liver, Kidney, Brain, Coagulation, Respiration, Circulation) and c). **High short-term mortality** (main cause of death in cirrhosis)

DIAGNOSTIC CRITERIA OF ACLF: ORGAN FAILURES. CLIF-CONSORTIUM ORGAN FAILURE SCORE.(CANONIC STUDY)

Organ/ System	Score = 1	Score = 2	Score = 3
Liver (mg/dl)	Bilirubin < 6	$6 \leq \text{Bilirubin} \leq 12$	Bilirubin >12
Kidney (mg/dl)	Creatinine <2	Creatinine $\geq 2 < 3.5$	Creatinine ≥ 3.5 or renal replacement
Brain (West-Haven)	Grade 0	Grade 1-2	Grade 3-4
Coagulation	INR < 2.0	$2.0 \leq \text{INR} < 2.5$	INR ≥ 2.5
Circulation	MAP ≥ 70 mm/Hg	MAP <70 mm/Hg	Vasopressors
Respiratory: PaO ₂ /FiO ₂ or SpO ₂ /FiO ₂	>300 >357	$\leq 300 - > 200$ >214- ≤ 357	≤ 200 ≤ 214

Values at study enrolment. Highlighted area reflects the definition of each organ failure.

Moreau et al, Gastroenterology 2013

OTHER IMPORTANT DIAGNOSTIC CRITERIA OF ACLF

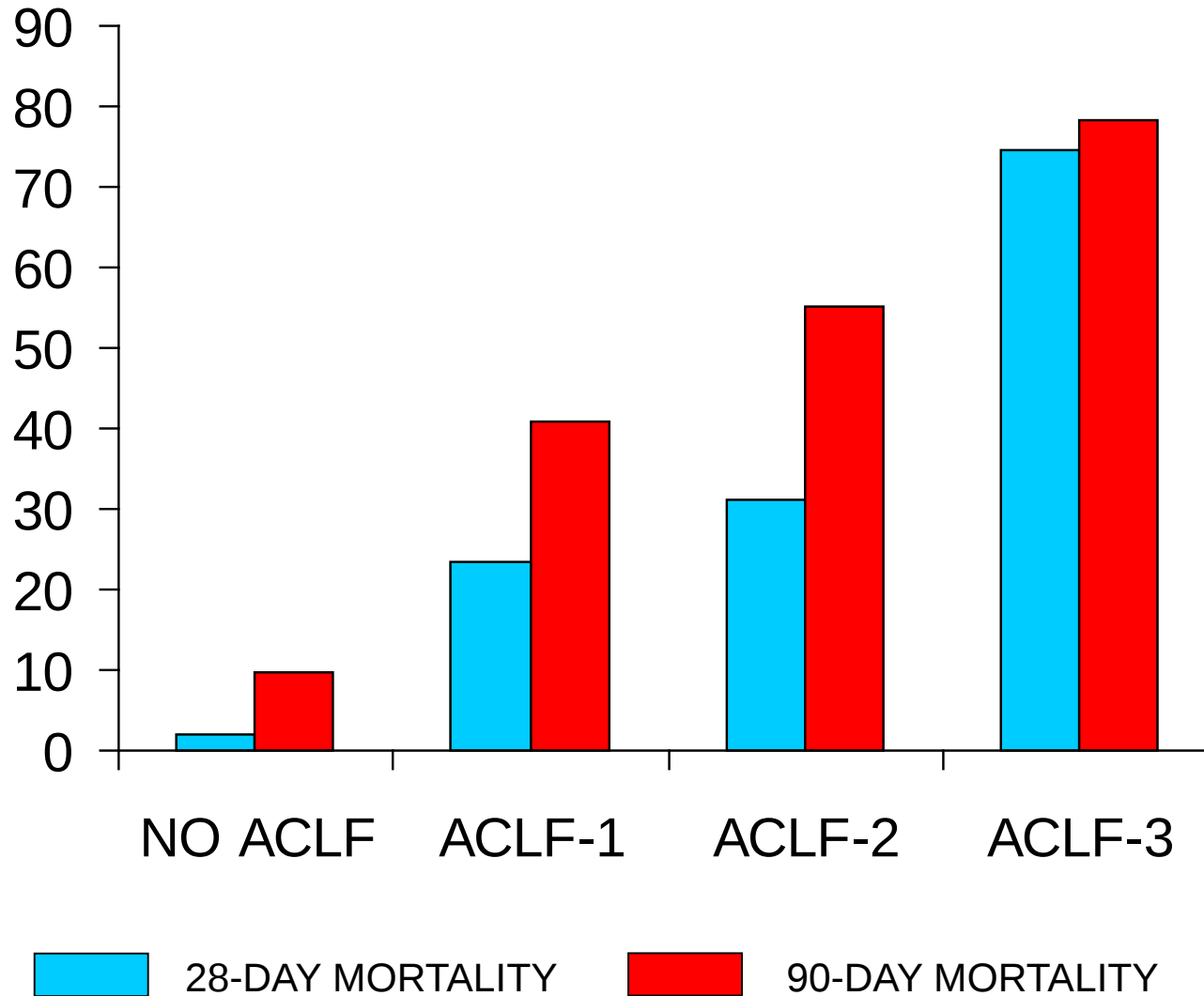
1. **High short-term mortality rate:** 28-day mortality rate > 15%*.
2. **Cerebral Dysfunction:** Grade 1-2 (West Haven) hepatic encephalopathy.
3. **Renal Dysfunction:** Serum creatinine 1.5- 1.9 mg/dl

* 50% mortality rate of septic shock

DIAGNOSIS AND GRADES OF ACLF (CANONIC Study)

	TX-FREE PATIENTS (N=1287)	28-DAY DEATH RATE	ACLF grades
No OF	879 (68.3%)	39/879 (4.4%)	} è No ACLF
Single non renal OF, creatinine <1.5 mg/dl, no HE	128 (9.9%)	8/128 (6.3%)	
Single renal failure	86 (6.68%)	16/86 (18.6%)	} è ACLF-1
Single non-renal OF, creatinine 1.5-1.9 mg/dL and/or grade 1-2 HE.	54 (4.1%)	15/54 (27.7%)	
2 OF	97 (7.5%)	31/97 (32.0%)	è ACLF-2
3 OF	25 (1.9%)	17/25 (68.0%)	} è ACLF-3
4-6 OF	18 (1,4%)	12/18 (88.9%)	

28-DAY AND 90-DAY MORTALITY RATES ASSOCIATED TO ACLF (Canonic Study)



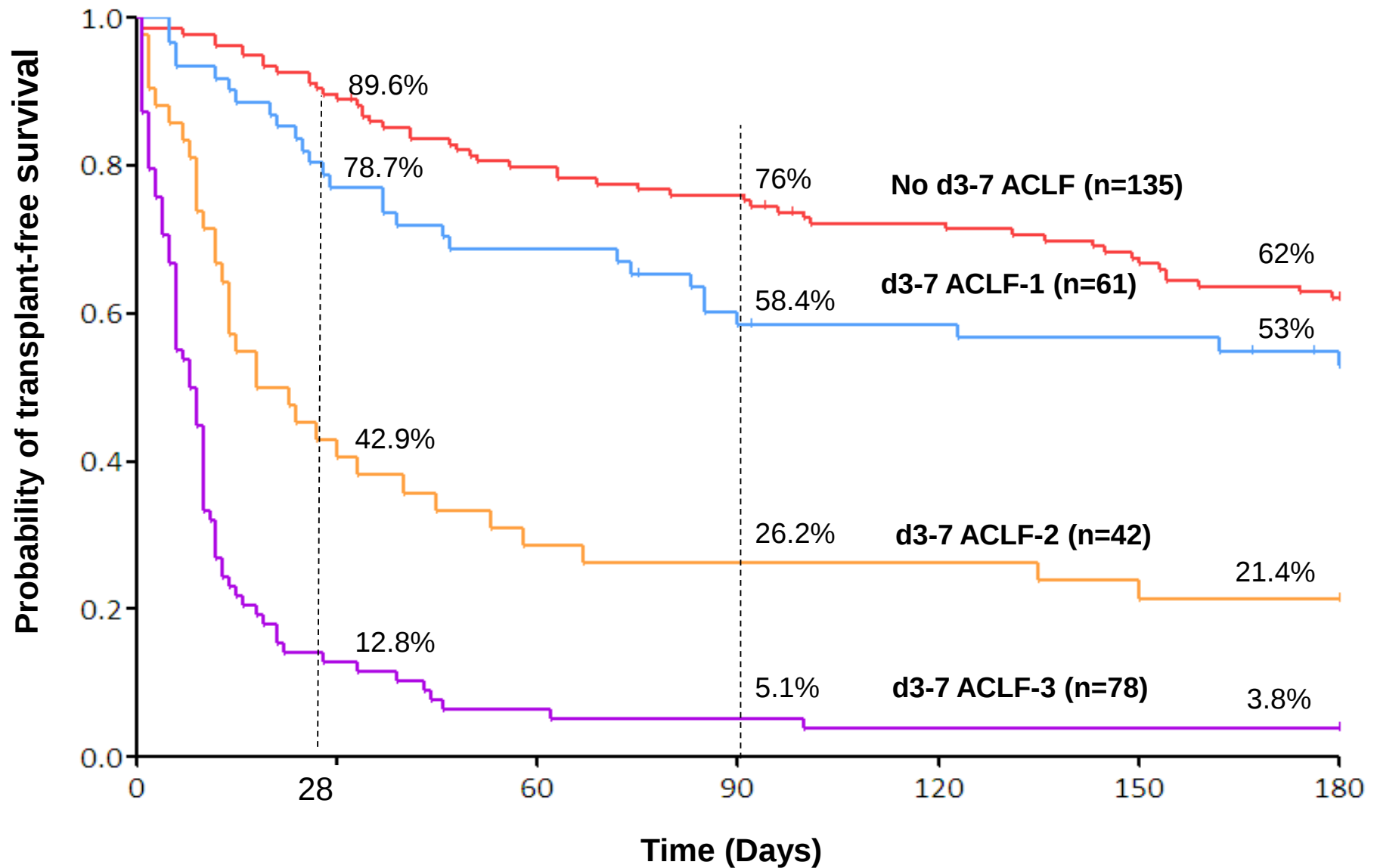
HEPATIC ENCEPHALOPATHY (HE), GI BLEEDING, ACLF AND MORTALITY

	mortality	28-day mortality	90-day
<u><i>Hepatic Encephalopathy</i></u>			
<u>No ACLF (n=285)</u>			
HE grades I-II (n=259)	5.8%		5.9%
HE grades III-IV (n=26)	7.6%		11.0%
<u>ACLF (n=174)</u>			
HE grades I-II (n=107)	30.0%		42.0%
HE grades III-IV (n=67)	50.7%		59.7%
<u><i>GI Bleeding</i></u>			
No ACLF (n=181)	2.8%		7.6%
ACLF (n=41)	46.3%		48.8%

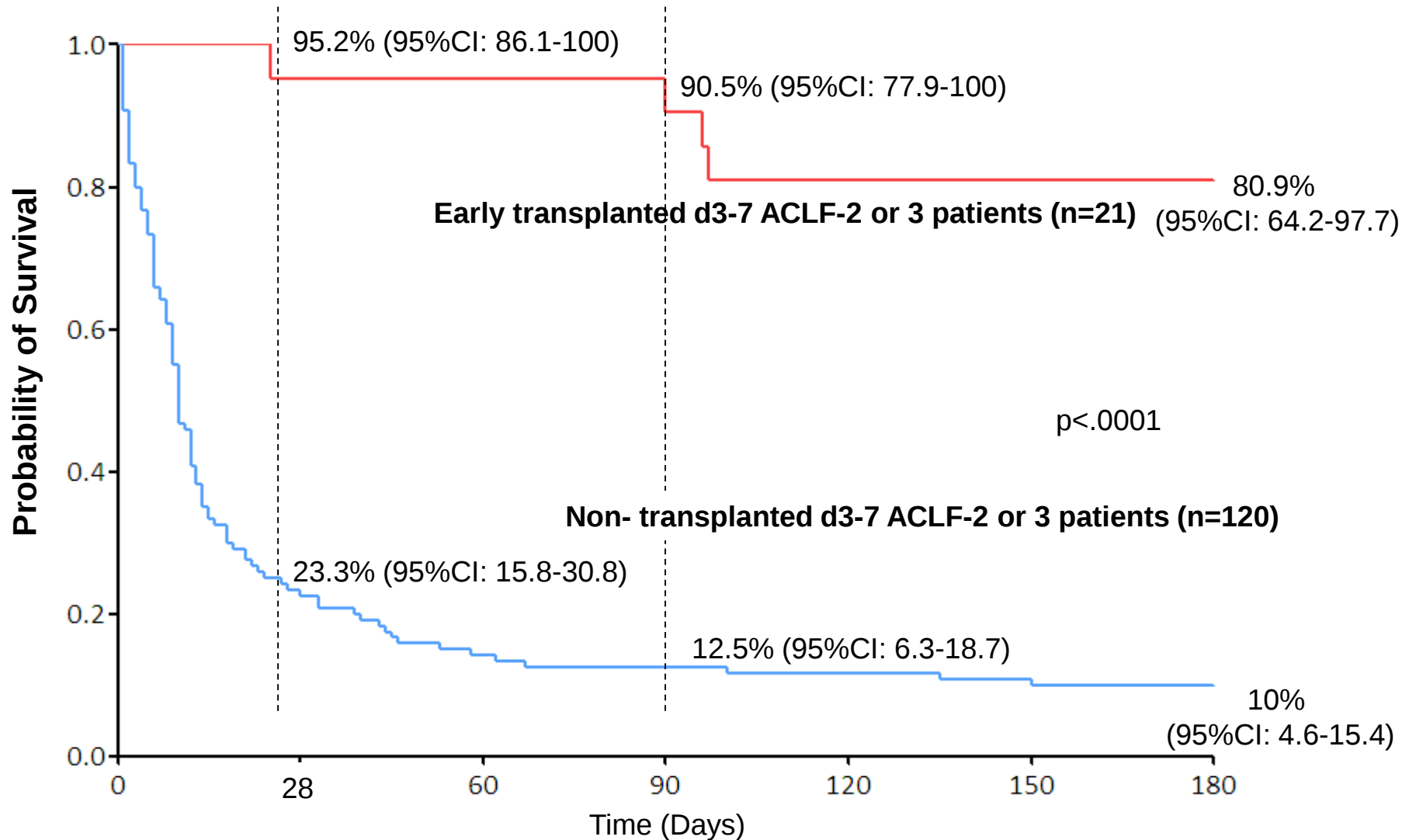
CLINICAL COURSE OF PATIENTS WITH ACLF (Canonic Study)

Initial Grade	Final Grade			
	No-ACLF	ACLF-1	ACLF-2	ACLF-3
ACLF-1 (202)	55%	24%	9%	12%
ACLF-2 (136)	34%	14%	25%	25%
ACLF-3 (50)	16%	4%	12%	68%

SURVIVAL ACCORDING TO DAY 3-7 CLINICAL COURSE



SURVIVAL PROBABILITY AFTER ACLF 2-3 DIAGNOSIS IN PATIENTS RECEIVING AND NOT RECEIVING AN EARLY LT (<28 DAYS)



FUTILITY CRITERIA FOR TREATMENT IN ACLF-3 PATIENTS ACCORDING TO THE NUMBER OF ORGAN FAILURES 3-7 DAYS AFTER DIAGNOSIS

<i>Number of organ failures 3-7 days after diagnosis</i>	<i>28-day Tx free mortality</i>	<i>90-day Tx free mortality</i>
0-1 (n=14)	1 (7%)	2 (14%)
2-3 (n=29)	16 (55%)	22 (75%)
4-6 (n=25)	24 (96%)	25 (100%)

SUGGESTED FUTILITY RULES IN ACLF ACCORDING TO THE EARLY CLINICAL COURSE

Diagnosis

ACLF

Medical management
ICU for organ support

Day 3-7

No ACLF

ACLF-1

ACLF-2

ACLF-3

Mortality rate (95% CI)
according to our data

Day 28	10% (5-16)	21% (11-32)	57% (42-72)	87% (80-95)
Day 90	24% (17-31)	42% (29-54)	74% (29-54)	95% (90-100)
Day 180	38% (30-46)	47% (34-60)	79% (66-91)	96% (92-100)

Assessment for regular LT

Assessment for early 28-day LT

Contraindication
for LT?

No

Yes

No

Yes

Regular LT

Early 28-day LT

Survival rate (95% CI)
according to our data

< 4 OFs and
CLIF-C ACLFs < 64* ≥ 4 OFs or
CLIF-C ACLFs > 64*

Day 180

85% (69-95)

58% (51-65)

79% (54-94)

35% (23-48)

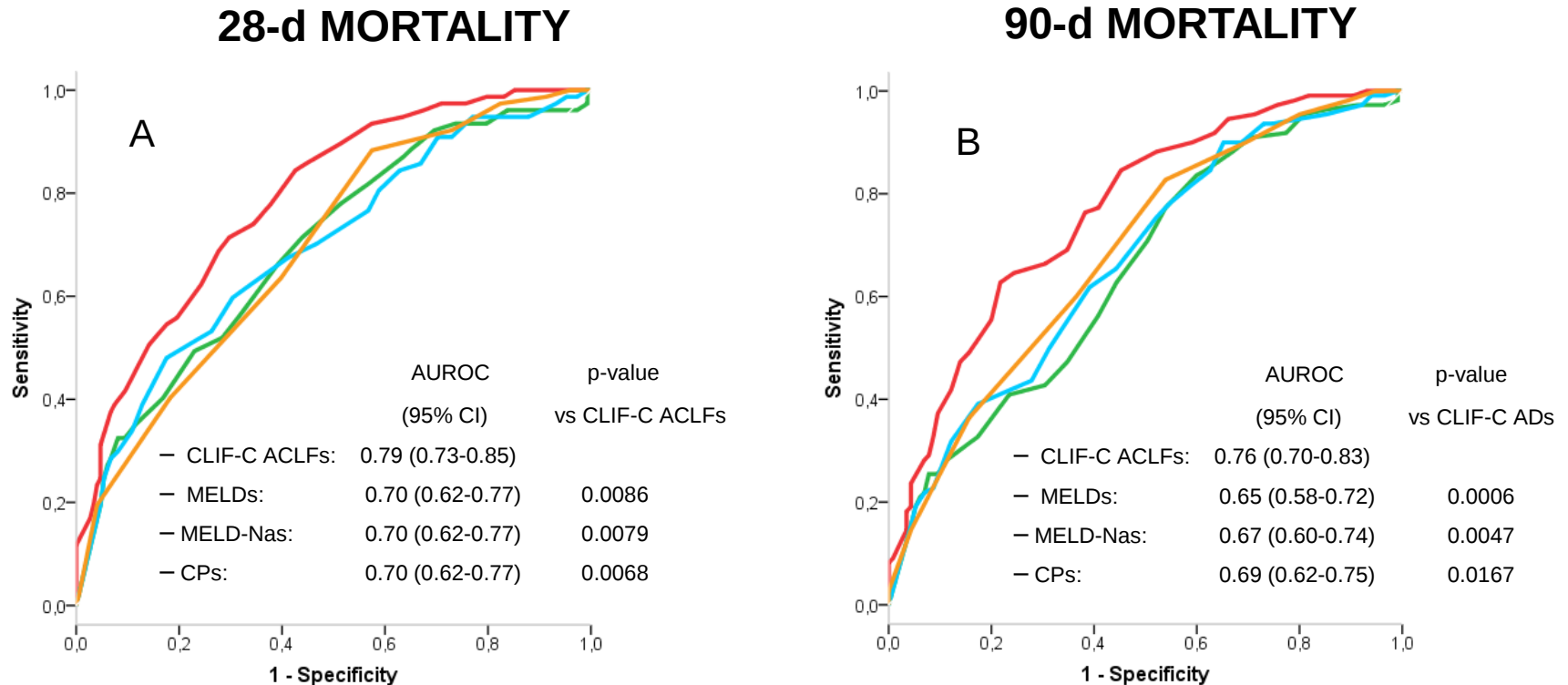
0% (0-10)

Continue treatment

Continue treatment

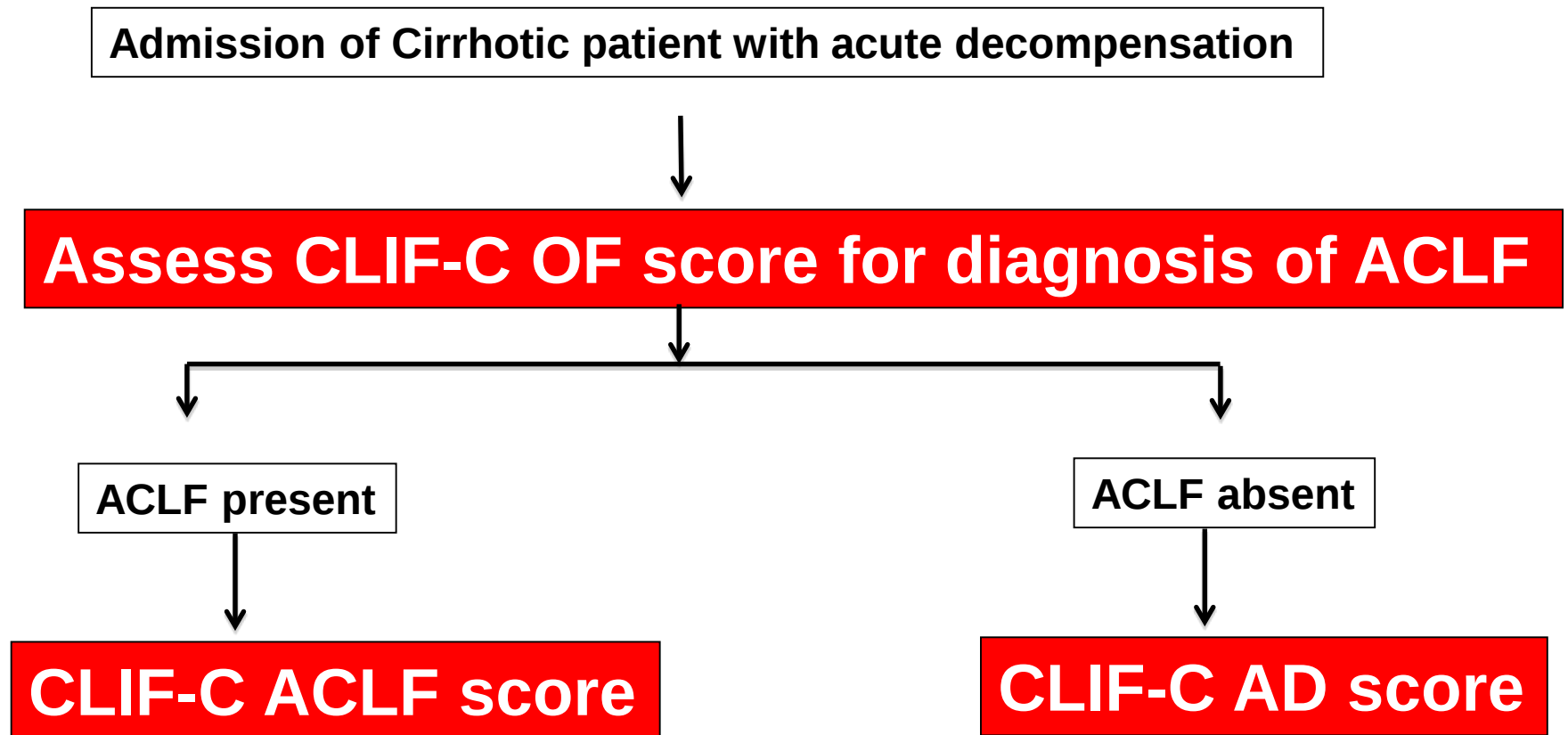
Futility

ACCURACY OF CLIF-C ACLF SCORE IN PREDICTING MORTALITY COMPARED TO OTHER LIVER SCORES



$$\text{CLIF-C ACLFs} = 10 \times [0.33 \times \text{CLIF-OFs} + 0.04 \times \text{Age} + 0.63 \times \ln(\text{WBC count}) - 2]$$

CLIF-C ACLF CLIF-C AD SCORES IN THE PROGNOSIS ASSESMENT OF DECOMPENSATED CIRRHOSIS



<http://www.clifconsortium.com/aclf-calculator/>

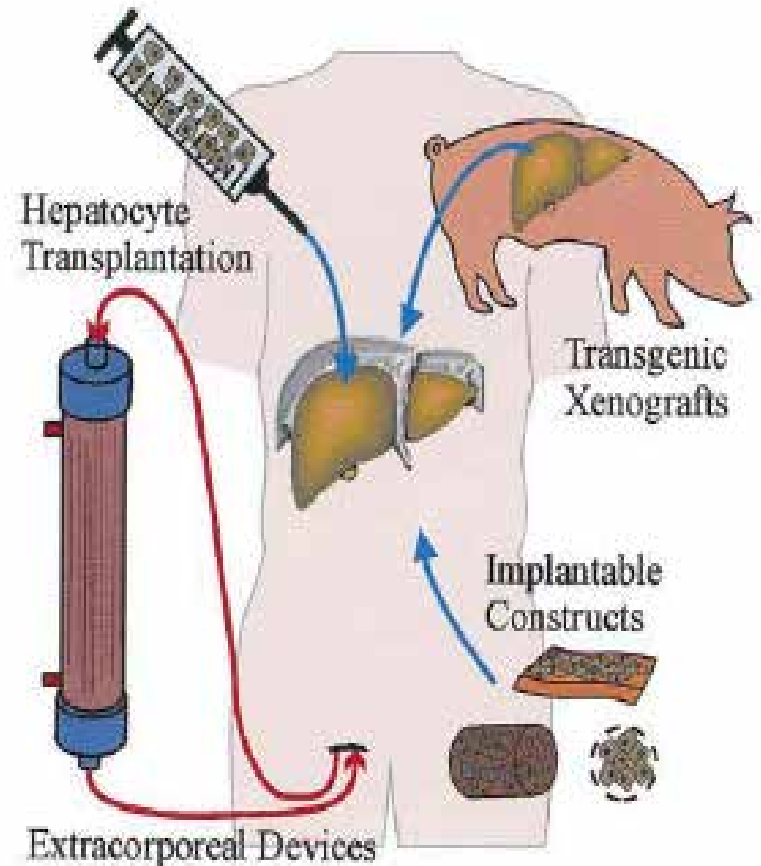
Acute-on-Chronic Liver Failure (ACLF) classification and expected mortality rates

CLIF-C ACLF Score and ACLF grade. Only for patients with ACLF

Score Formulae		
	DATA	SCORES
Bilirubin	mg/dl	Liver score
		Liver failure ☒ Yes ☐ No
Serum Creatinine	mg/dl	Kidney score
Renal replacement therapy	☐ Yes ☐ No	Renal failure ☒ Yes ☐ No
Use of vasopressors (Hepatorenal syndrome indication)	☐ 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	mm/Hg	Circulation score
Use of vasopressors (Circulatory failure indication)	☐ Yes ☐ No	Circulation failure ☒ Yes ☐ No
Select one	☒ PaO ₂ (preferred) ☐ SpO ₂	Lung score
		Respiratory failure ☒ Yes ☐ No
FiO ₂	%	
Mechanical Ventilation	☐ Yes ☐ No	
Total Number Failures		
CLIF Organ Failure Score		

LIVER SUPPORT SYSTEMS

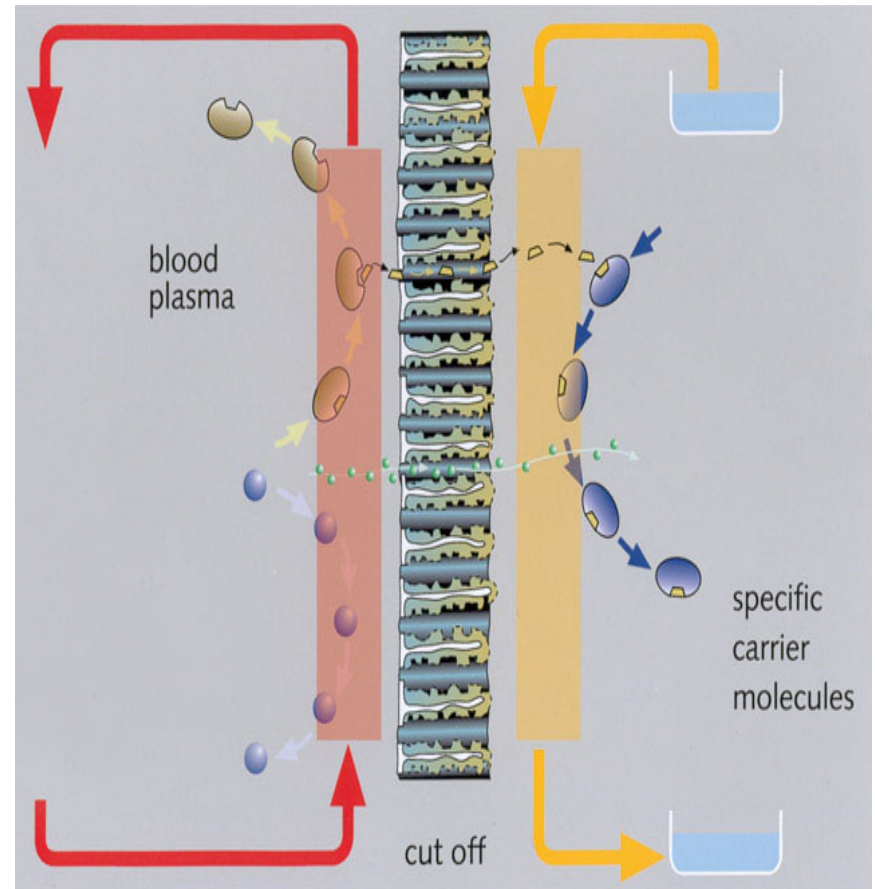
- Detoxification systems:
 - Hemodialysis
 - Hemofiltration
 - Plasma exchange
 - Albumin dialysis (MARS)**
 - Prometheus (PSF)**
- Bioartificial systems
- Hepatocyte transplantation



NON-BIOLOGICAL ARTIFICIAL LIVER SUPPORT DEVICES

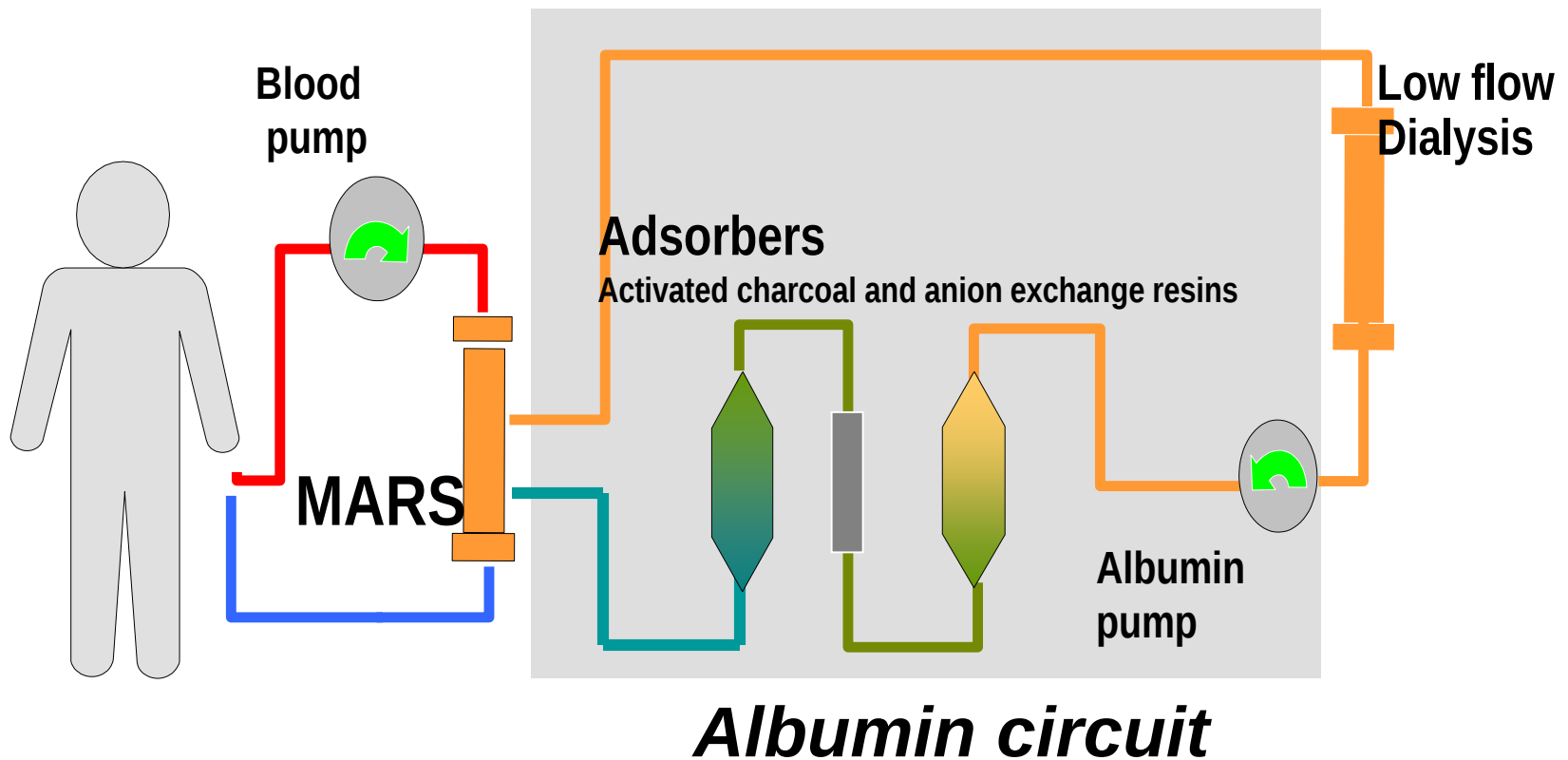
**Molecular adsorbent
recirculating system
(MARS)**

**Fractionated plasma
separation and adsorption
(Prometheus)**

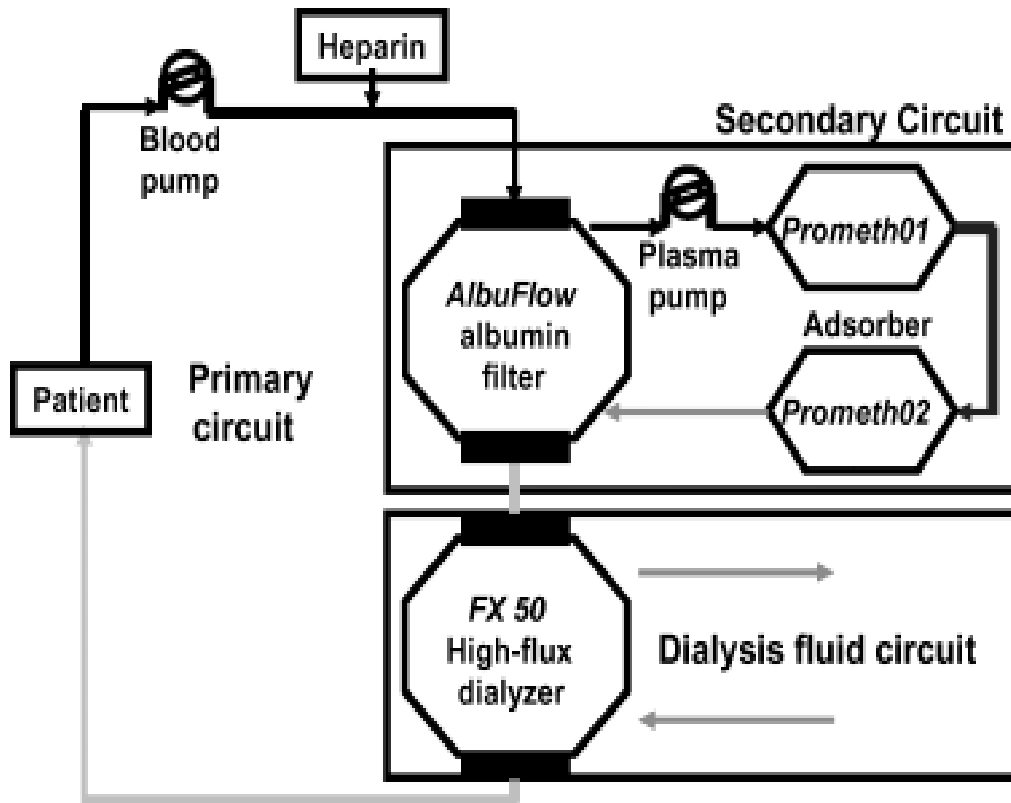


*They can clear water soluble toxins but also,
in contrast to hemodialysis, albumin-bound toxins*

MARS SYSTEM



PROMETHEUS SYSTEM

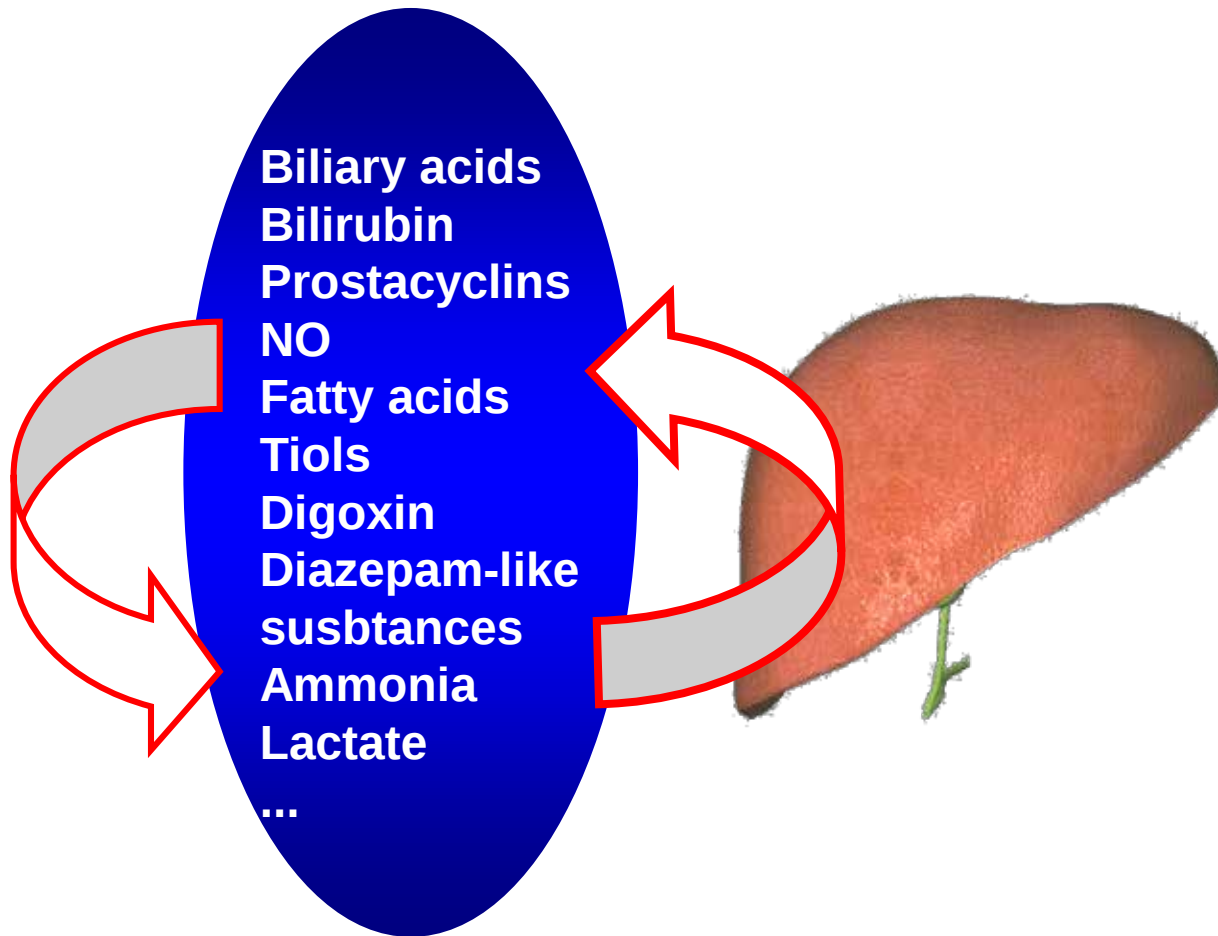


Albumin circuit

**High flux
hemodialysis**

ACUTE LIVER FAILURE

“THE TOXIC THEORY”



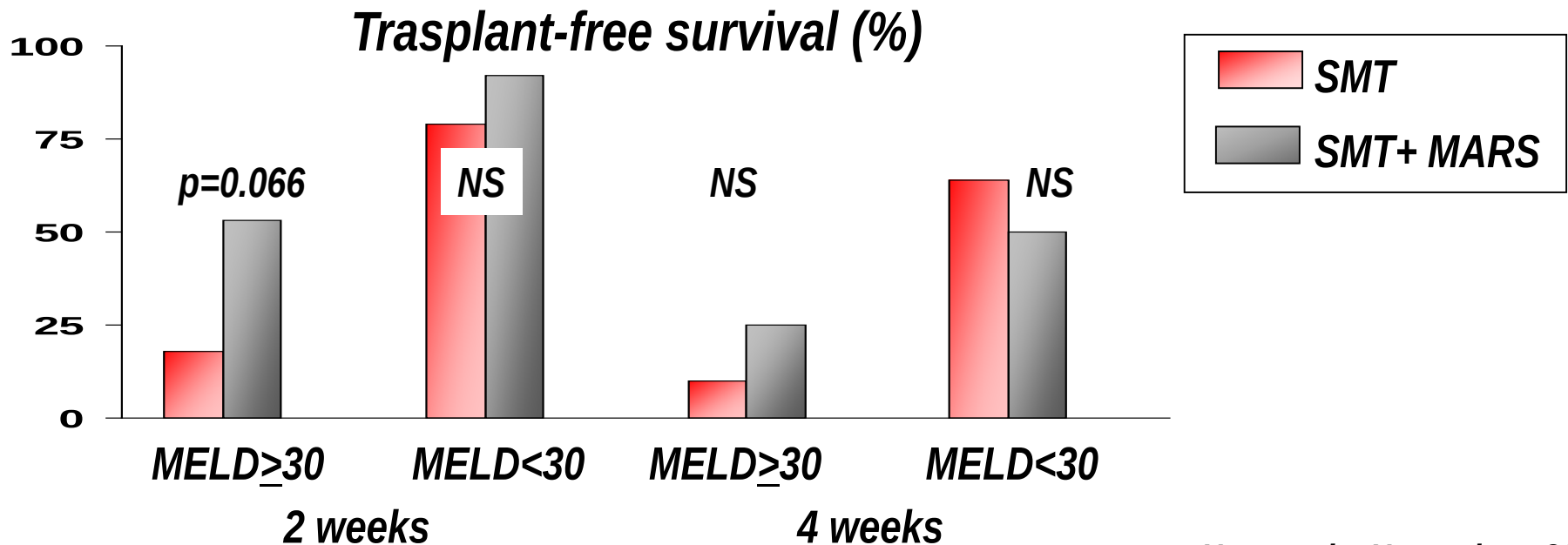
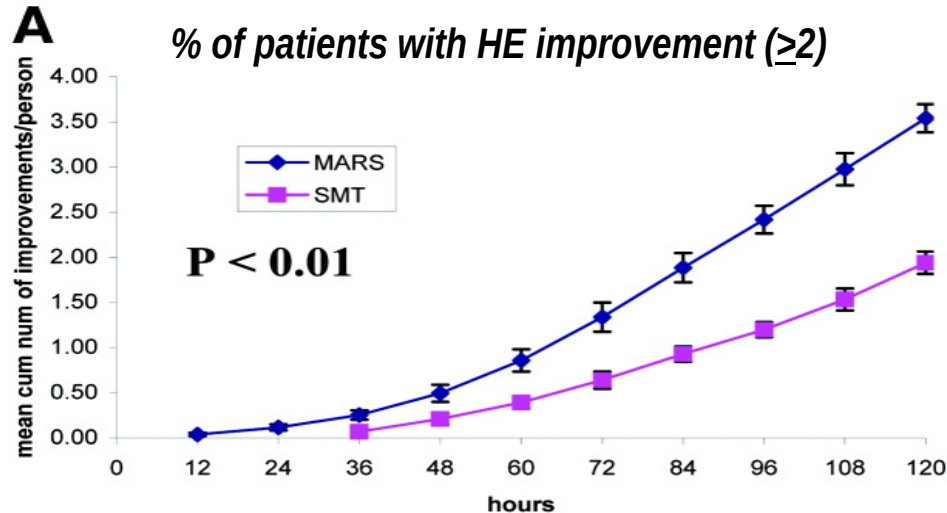
Accumulation of albumin-bound and water soluble (vasoactive) toxins

Liver injury
Necrosis
Apoptosis

Dysfuncion:

- Cerebral
- Renal
- Circulatory
- Immune

MARS in AoCLF (HE) III/IV

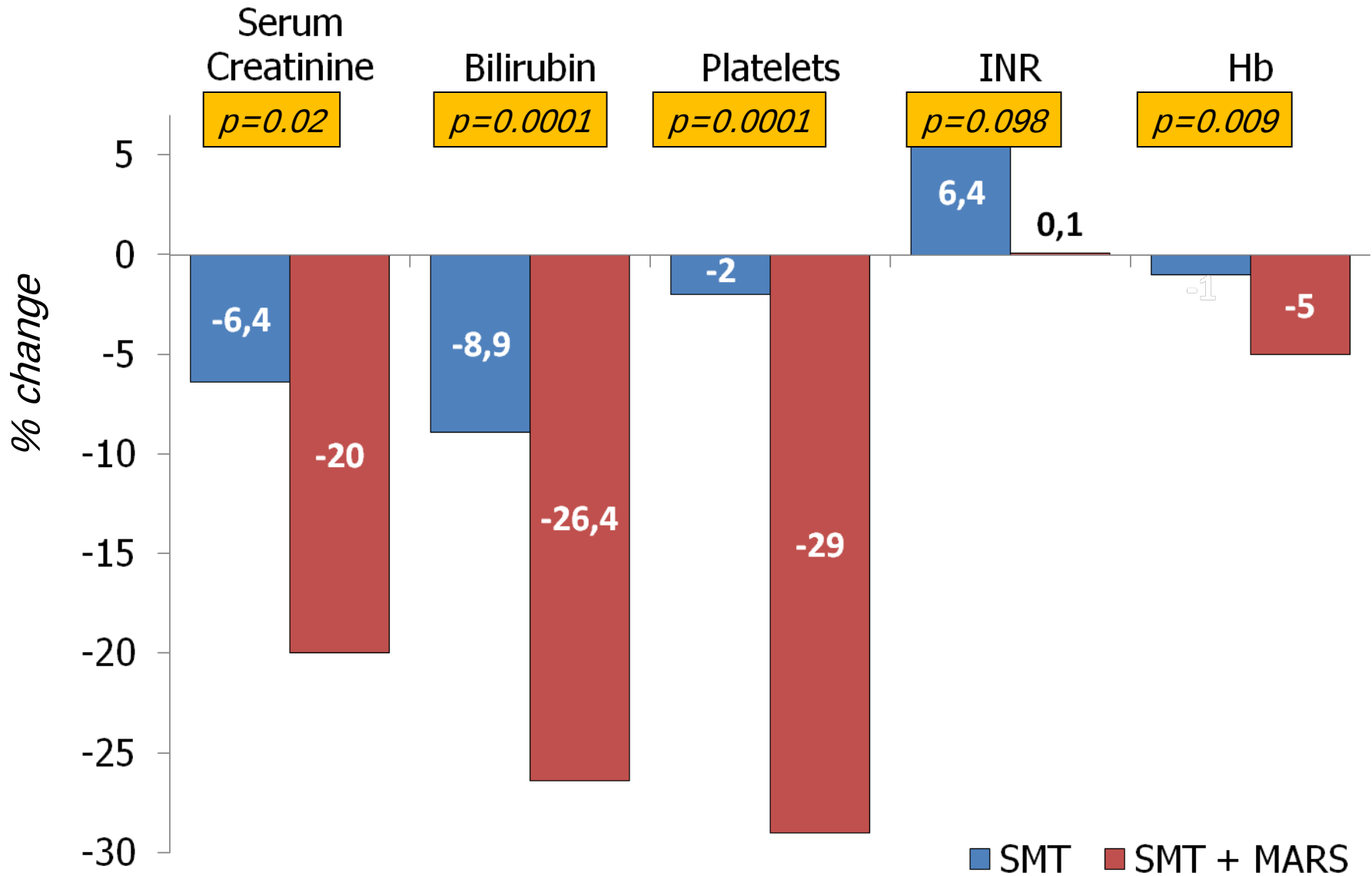


ALBUMIN DIALYSIS IN ACLF

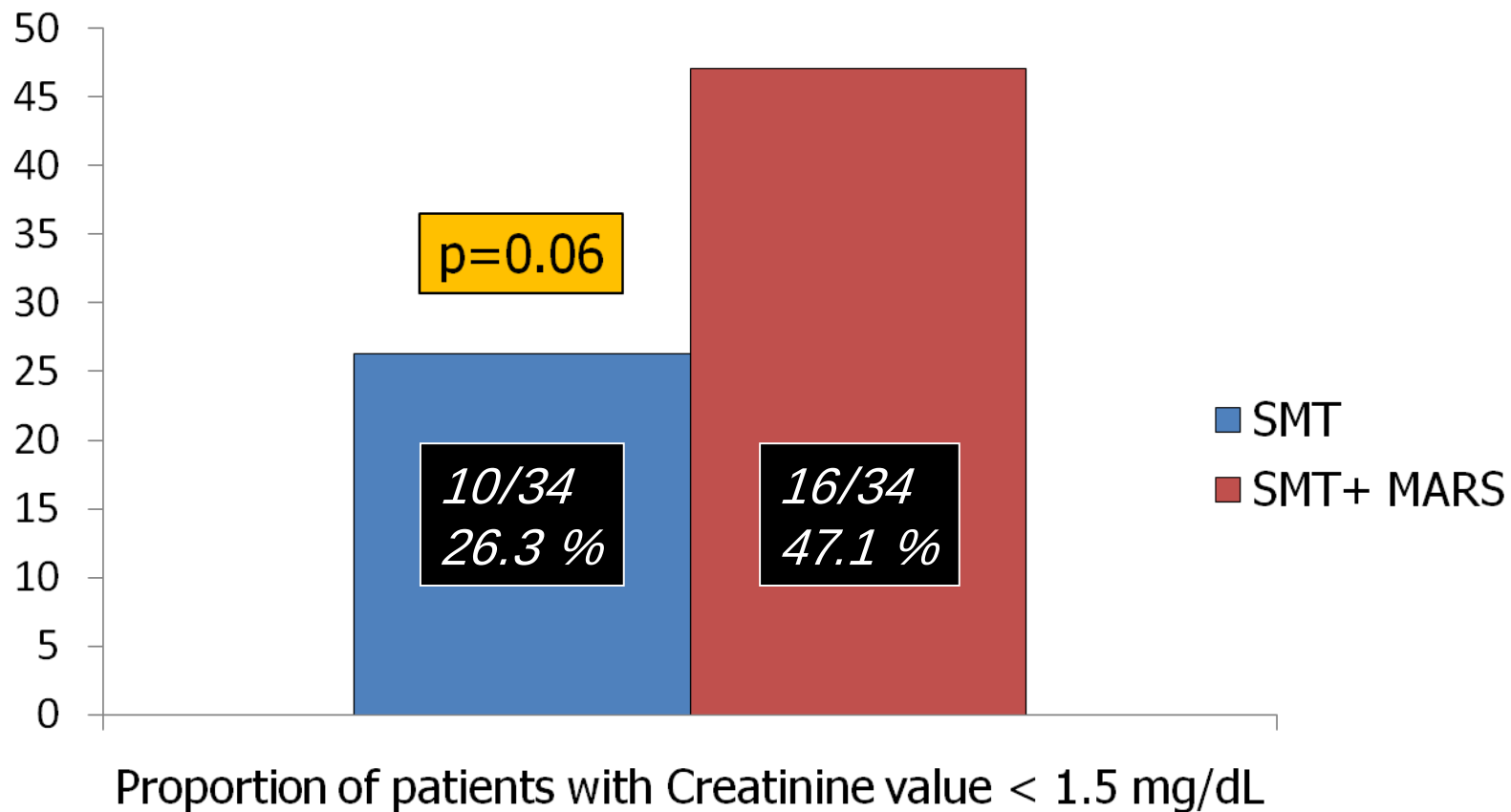
MARS RELIEF TRIAL

- ü 189 patients
- ü Definition of ACLF: cirrhosis + bilirubin >5 mg/dl and HRS or HE $\geq$ 2 or serum bilirubin >20 mg/dl:
 - MARS: n= 90
 - SMT: n= 89
- ü Primary endpoint: transplant-free survival
- ü Secondary endpoints: HE and some analytical changes

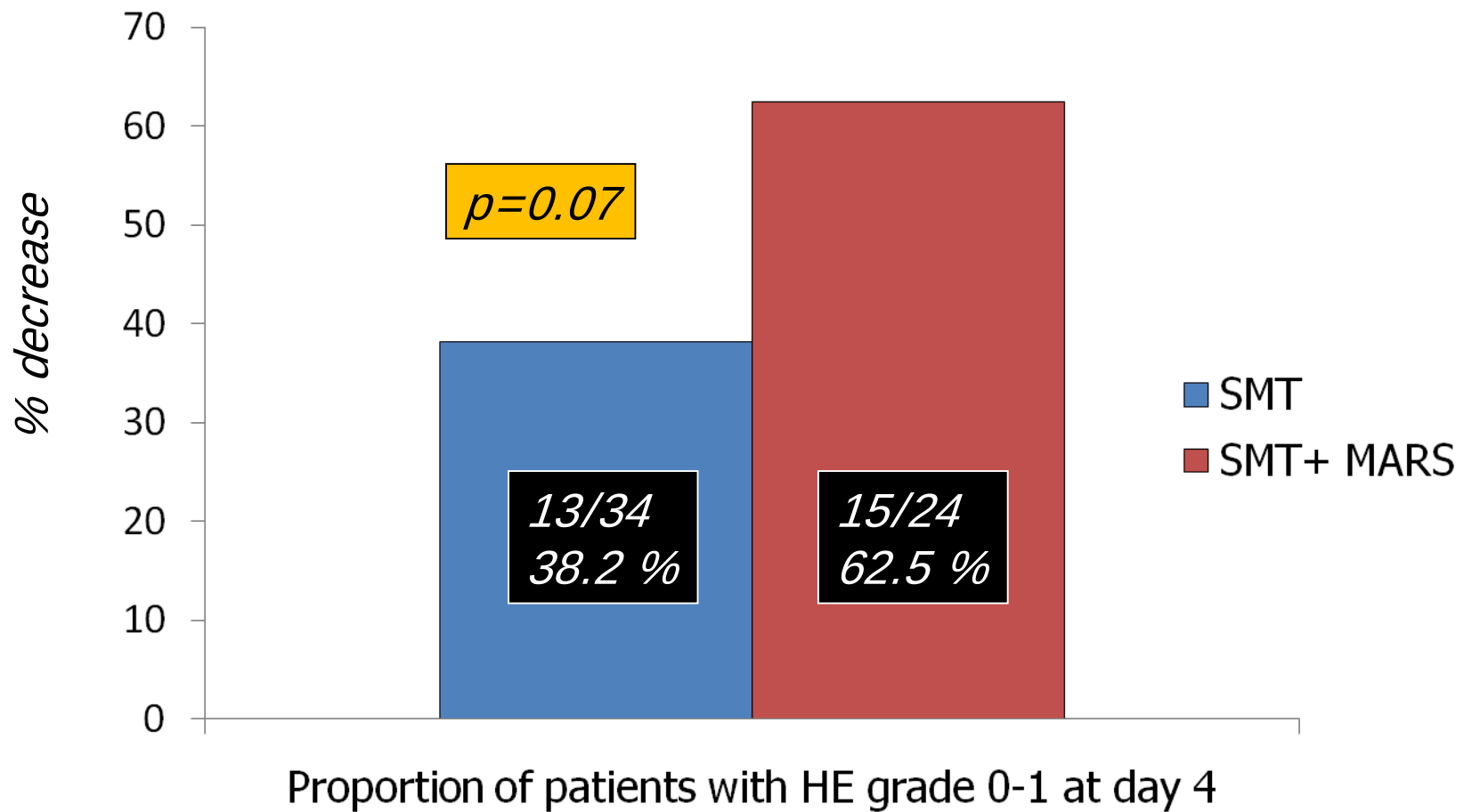
CHANGES IN BASELINE PARAMETERS: DAY 4



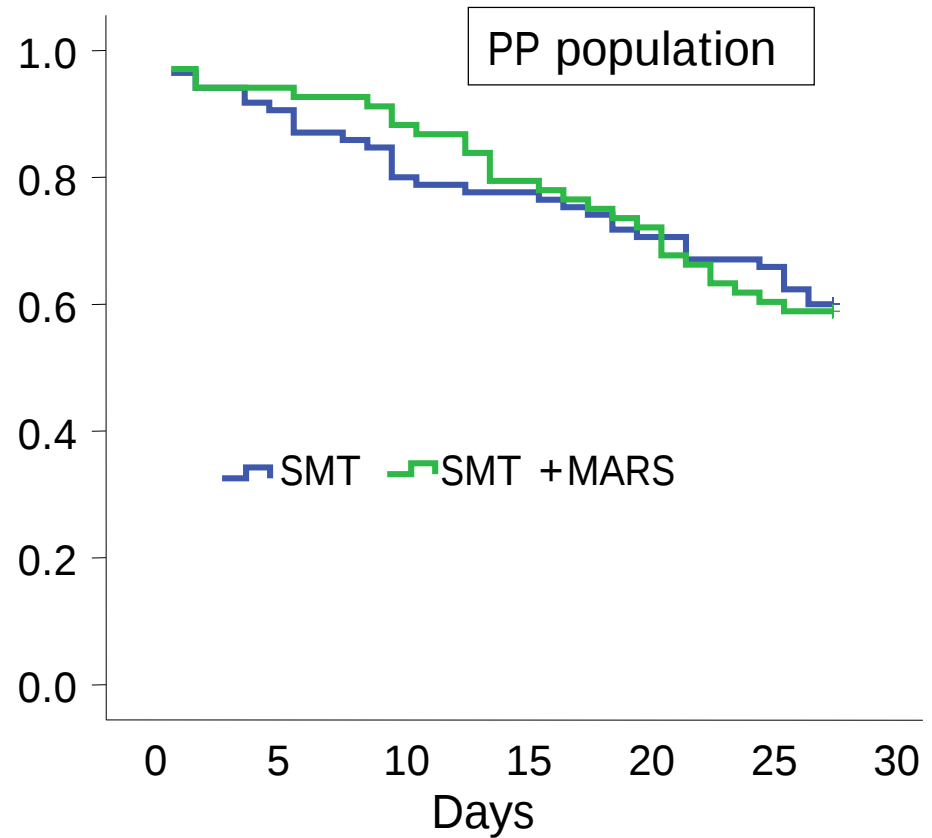
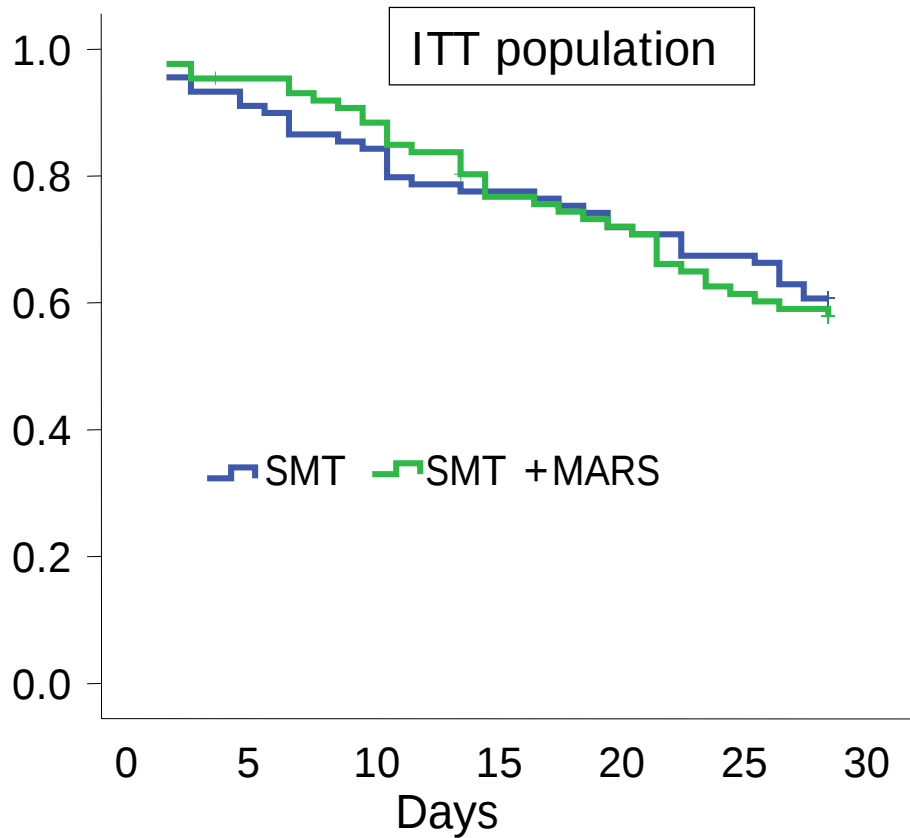
EFFECTS ON RENAL FUNCTION IN PATIENTS WITH HRS AT DAY 4



EFFECTS ON HEPATIC ENCEPHALOPATHY AT DAY 4



EFFECT OF MARS ON 28 DAYS TRANSPLANT-FREE SURVIVAL



ITT population
Overall 28 days mortality:
SMT: 39.3 %
SMT + MARS: 41.4 %
Log-rank test: P=0.79

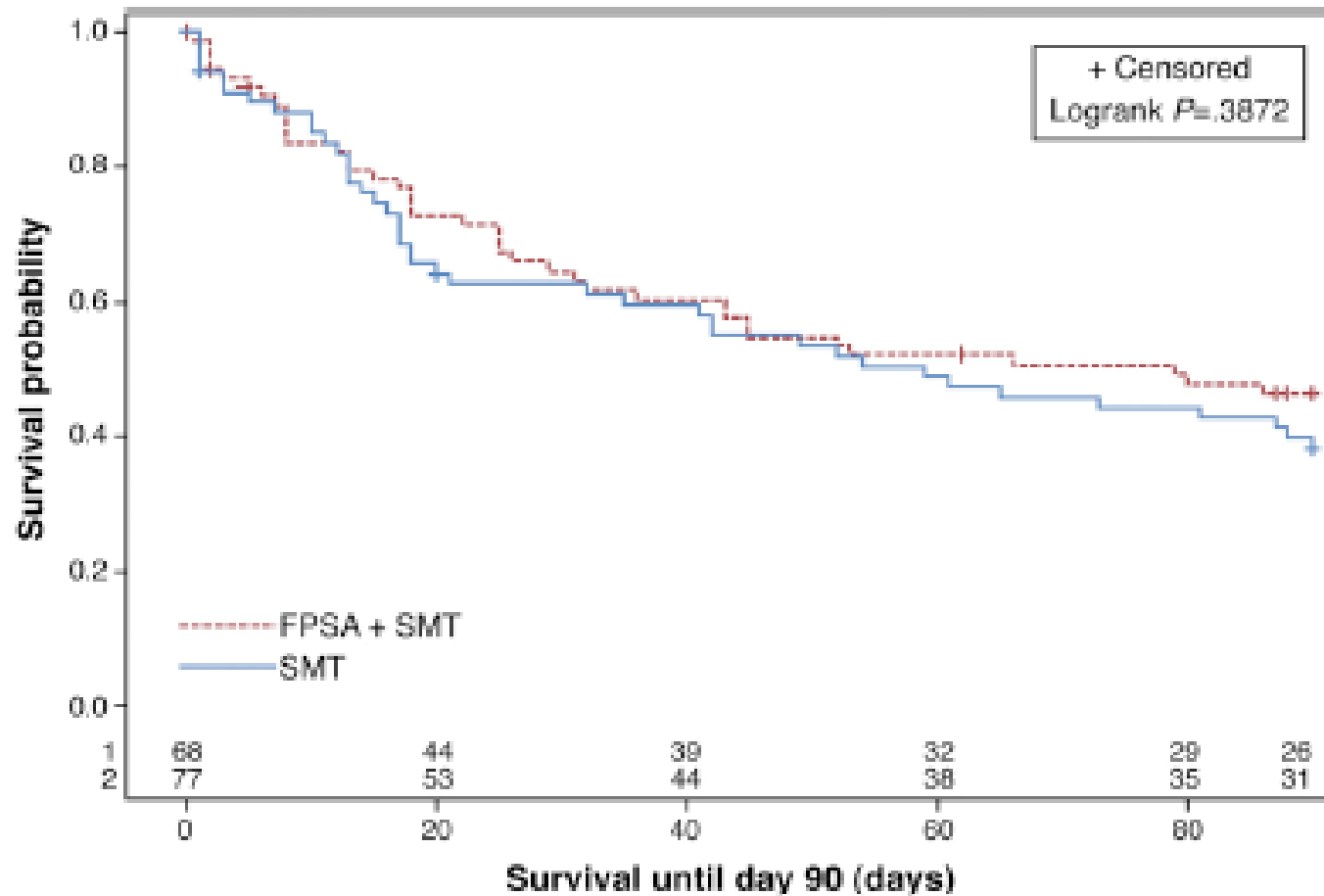
PP population
Overall 28 days mortality:
SMT: 40 %
SMT + MARS: 41.2 %
Log-rank test: P=0.88

ALBUMIN DIALYSIS IN ACLF

PROMETHEUS TRIAL

- ü 145 patients
- ü Definition of ACLF: CH + bilirubin >5 mg/dl + Child-Pugh >10 points
- ü Number of patients:
 - 68 SMT
 - 77 SMT+FPSA (fractionated plasma separation and adsorption)
- ü Primary endpoint: 28 day survival
- ü Predefined subanalysis in type-1 HRS and in high MELD score (> 30 p) groups

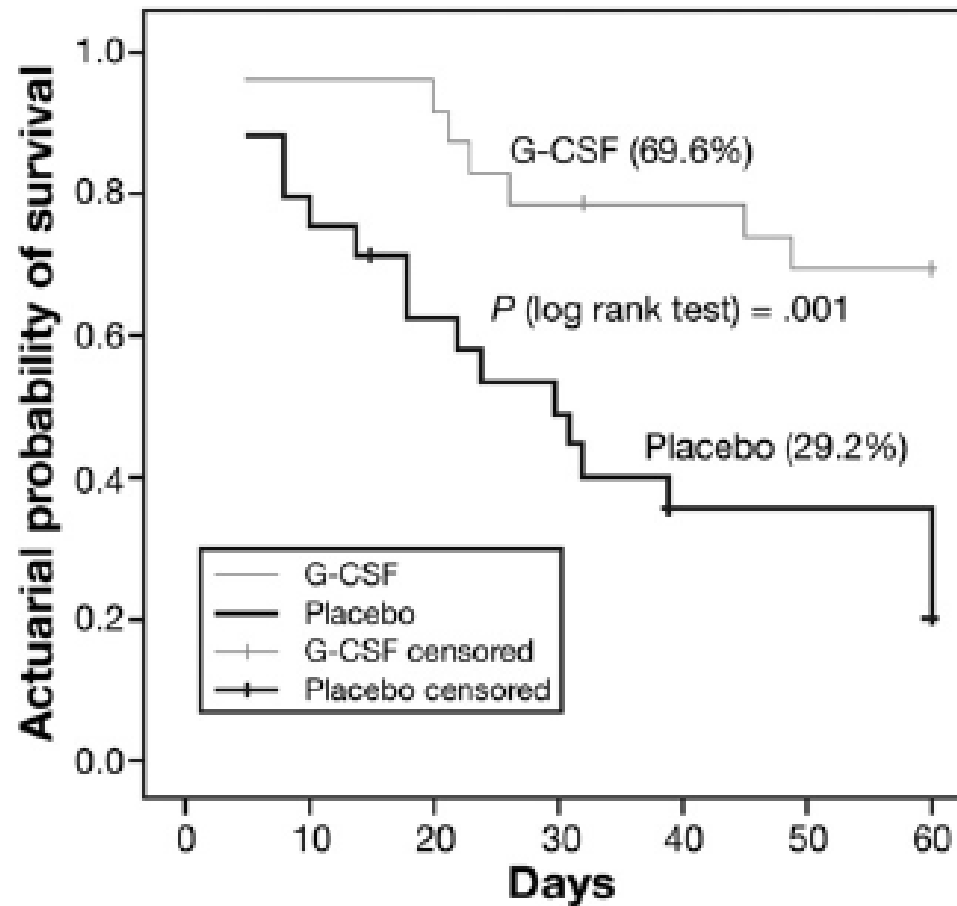
PROMETHEUS RCT: 90-day survival



GRANULOCYTE COLONY-STIMULATING FACTOR IN ACLF

- ü 47 patients
- ü Definition of ACLF: bilirubin ≥ 5 mg/dl and INR ≥ 1.5 and ascites or hepatic encephalopathy (APASL criteria)
- ü Exclusion criteria: sepsis, MOF, grade 3-4 hepatic encephalopathy
- ü Blinded placebo controlled trial:
 - 23 G-CSF 5 μ g/Kg SBC (12 doses)+SMT
 - 24 SMT
- ü Primary endpoint: 60 day survival

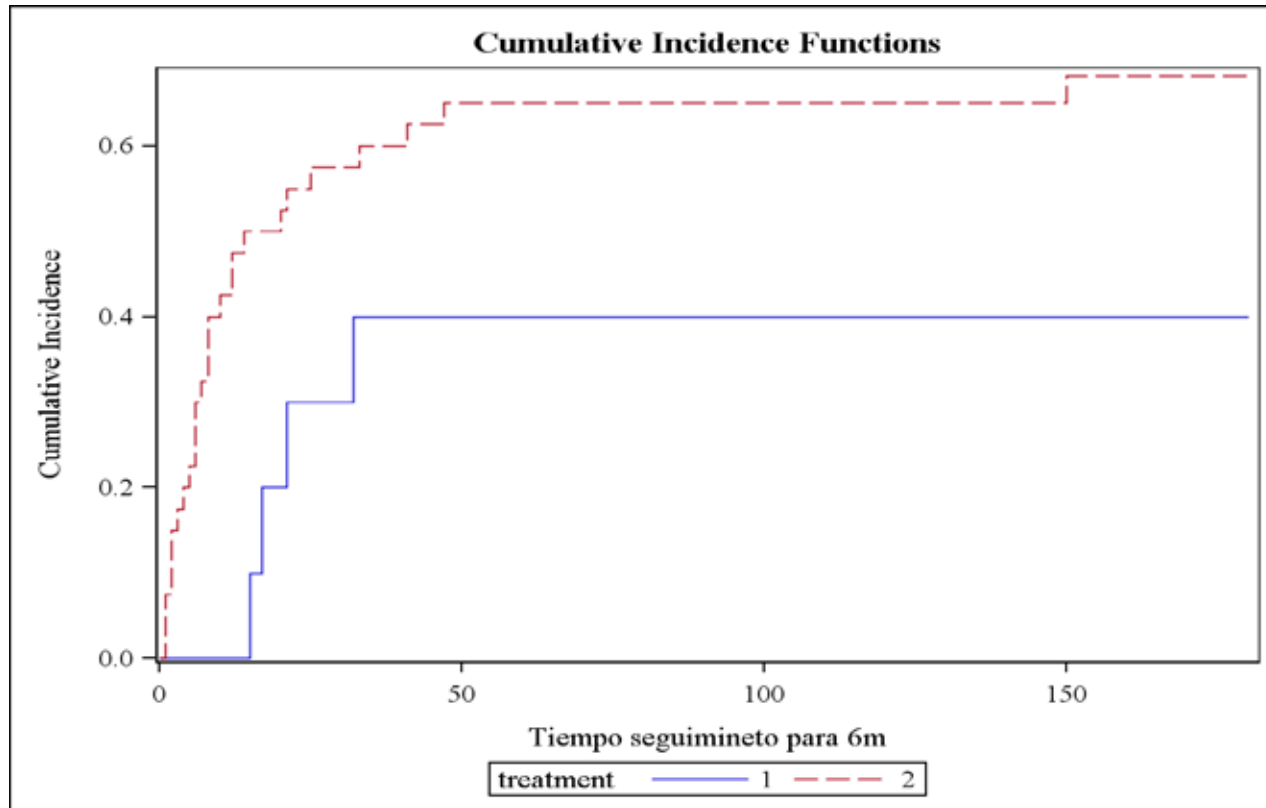
GRANULOCYTE COLONY-STIMULATING FACTOR IN ACLF



PLASMA EXCHANGE IN ACLF

- Open label pilot study: 10 patients
- Inclusion criteria: ACLF defined by acute deterioration of liver function within the last 2-4 weeks with serum bilirubin ≥ 5 mg/dl and hepatic encephalopathy ($\geq$ grade 2) and/ or renal failure (serum creatinine ≥ 2 mg/dl).
- Treatment schedule: 6 sessions/patient in 10 days; 5% albumin as the main replacement fluid ($\cong 70\%$ of plasma exchanged)
- Main endpoint: safety

EFFECTS OF PLASMA EXCHANGE ON THE PROBABILITY OF DEATH



	Plasma exchange	Controls	
	10 cases	40 controls matched by CLIF-c	Survival p-value
28-day mortality a 28 días	3(30,0)	23(57,5)	0,077
90 day mortality	4(40,0)	26(65,0)	0,098
6 month mortality	4(40,0)	27(67,5)	0,078

CLINICAL CASE 1

A 52 year old man with alcoholic cirrhosis, previous history of ascites, on treatment with diuretics and actively working as civil engineering, was admitted to hospital with CA pneumonia and rapid deterioration of his clinical condition. On admission the patient showed ascites, jaundice (bilirubin 21 mg/dl), grade III hepatic encephalopathy, renal failure (serum creatinine 2.2 mg/dl) and coagulopathy (INR: 2.6)

Grade of ACLF at admission? Grade 3

Number of organ failures?

No vasopressors, MAP: 72 mmHg, PaFiO₂: 225

Number of organ failures: 4

Prognosis? 89% mortality at 28 days

CLINICAL CASE 1

The patient was admitted to the ICU: IV antibiotics, mechanical ventilation due to hepatic encephalopathy

Four days later: progressive impairment of liver (bilirubin 30 mg/dl), renal (RRT), respiratory (PaFiO₂: 150) and vascular function (noradrenalin), INR: 2.7

Futility?

CLIF-C ACLF score?

Score Formulae

DATA		SCORES	
Bilirubin	30 mg/dl	Liver score	3
Serum Creatinine	2.2 mg/dl	Liver failure	☒ Yes ☐ No
Renal replacement therapy	☒ Yes ☐ No	Kidney score	3
Use of vasopressors (Hepatorenal syndrome indication)	☒ Yes ☐ No	Renal failure	☒ Yes ☐ No
West-Haven grade for HE	☐ 0 ☐ 1 ☒ 2 ☐ 3 ☐ 4	Brain score	3
INR	2.6	Cerebral failure	☒ Yes ☐ No
MAP	72 mm/Hg	Coagulation score	3
Use of vasopressors (Circulatory failure indication)	☒ Yes ☐ No	Coagulation failure	☒ Yes ☐ No
Select one	☒ PaO ₂ (preferred) ☐ SpO ₂	Circulation score	3
FiO ₂	80 %	Circulation failure	☒ Yes ☐ No
Mechanical Ventilation	☒ Yes ☐ No	Lung score	3
Reason for Mechanical Ventilation	Both	Respiratory failure	☒ Yes ☐ No
Total Number Failures	6		
CLIF Organ Failure Score	12		
ACLF-Grade 3		The patient has ACLF	
Reset		Compute	

6 OF
CLIF-C ACLF score: 79



Treatment withdrawal

Probability of dying

Age	52 years
White-cell count	20.0 10 ⁹ cells/L*
CLIF-C ACLF Score	79
Probability of dying at 1 month	100 %
Probability of dying at 3 month	100 %
Probability of dying at 6 month	100 %
Probability of dying at 12 month	100 %
Reset Compute	

* If the patient has 8,300 leucocits/mm3, this must be introduced as 8.3

CLINICAL CASE 2

A 56 year old man with alcoholic cirrhosis, no previous decompensations. He was admitted to hospital with jaundice and ascites: severe alcoholic hepatitis (transjugular biopsy proven).

On admission the patient showed ascites, jaundice (bilirubin 34 mg/dl), grade I hepatic encephalopathy and renal failure (serum creatinine 2.03 mg/dl). No vascular, respiratory or coagulation failure (INR: 2.4)

AH scores: Maddrey Discriminant Function: **112**, MELD: **36**, ABIC score: **10.85**.

Grade of ACLF? Grade 2

Tx: steroids+NAC

CLINICAL CASE 2

After 1 week of steroid treatment: ascites, bilirubin 44 mg/dl, grade I hepatic encephalopathy and renal dysfunction (serum creatinine 1.6 mg/dl). No vascular, respiratory or coagulation failure (INR: 2.37).

Lille score: 0.995

Tx: stop steroids

CLIF-C ACLF score? 63 points but just 1 OF

Tx: Plasma exchange therapy

Score Formulae

DATA		SCORES	
Bilirubin	44 mg/dl	Liver score	3
Serum Creatinine	1.69 mg/dl	Liver failure	☒ Yes ☐ No
Renal replacement therapy	☐ Yes ☒ No	Kidney score	1
Use of vasopressors (Hepatorenal syndrome indication)	☐ Yes ☒ No	Renal failure	☒ Yes ☐ No
West-Haven grade for HE	☐ 0 ☒ 1 ☐ 2 ☐ 3 ☐ 4	Brain score	2
INR	2.37	Cerebral failure	☒ Yes ☐ No
MAP	68 mm/Hg	Coagulation score	2
Use of vasopressors (Circulatory failure indication)	☐ Yes ☒ No	Coagulation failure	☒ Yes ☐ No
Select one	☐ PaO ₂ (preferred)	Circulation score	2
	☒ SpO ₂	Circulation failure	☒ Yes ☐ No
FiO ₂	35 %	Lung score	2
Mechanical Ventilation	☐ Yes ☒ No	Respiratory failure	☒ Yes ☐ No
Total Number Failures		1	
CLIF Organ Failure Score		12	
ACLF-Grade 1		The patient has ACLF	
Reset		Compute	

Probability of dying	
Age	56 years
White-cell count	27.0 10 ⁹ cells/L*
CLIF-C ACLF Score	63
Probability of dying at 1 month	68 %
Probability of dying at 3 month	84 %
Probability of dying at 6 month	87 %
Probability of dying at 12 month	90 %

CONCLUSIONS

- ü ACLF is not a “terminal event”. Its prognosis depends on the severity of systemic inflammation and on the number of organ failures (not on the precipitating event).
- ü It is especially severe in patients without prior decompensation.
- ü One-third of patients die within 28 days
- ü It is a highly dynamic and potentially reversible condition.

CONCLUSIONS

- ü Prognosis is better determined after initial intervention (3-7 days): evaluation of the number of OF and CLIF-C ACLF score.
- ü MARS improves HE in ACLF but has no impact on survival (as Prometheus)
- ü Liver transplantation is the only effective therapy
- ü Need for new treatments (MSC therapy, bioartificial liver support systems...) and for confirmatory studies (G-CSF, plasma exchange)