

# La suppléance hépatique au cours de la décompensation de la cirrhose

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# Liver Failure

Acute / Acute on chronic

Optimal Medical Care

Liver Support Systems

Bridge

Liver Regeneration

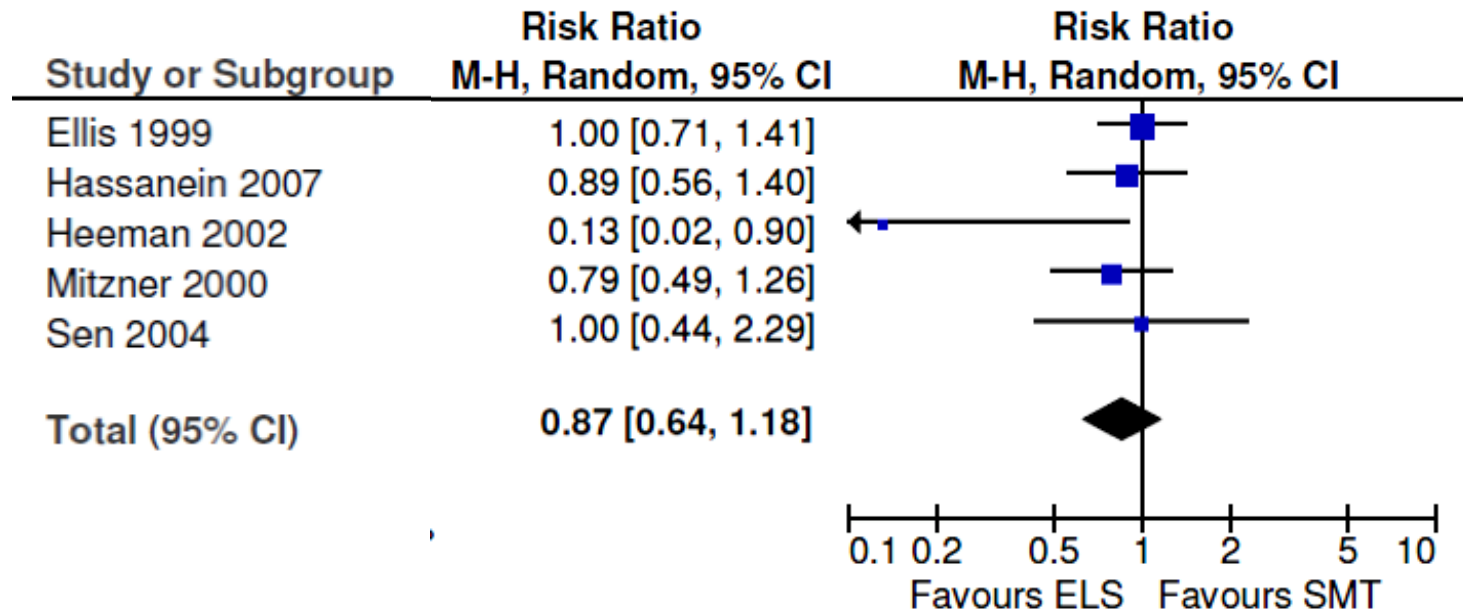
Liver Recompensation

Liver Transplantation

Recovery/Survival

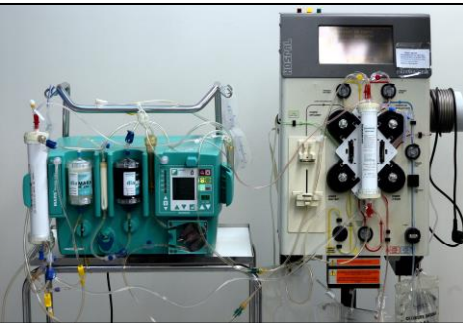
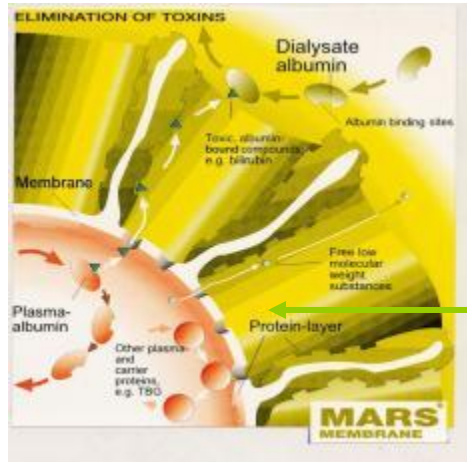
Patient improvement  
Neurological  
Hemodynamic  
Biological  
Liver, kidney  
Inflammation/Sepsis

# Meta-analysis in Acute on Chronic Liver Failure

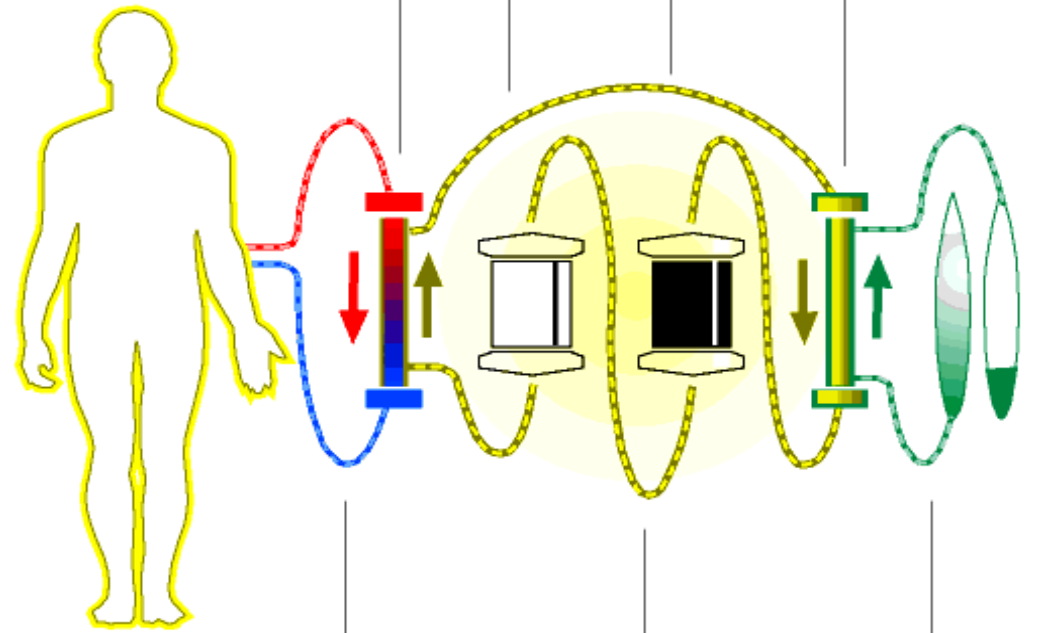


ELS: Extracorporeal Liver Support  
SMT: Standard Medical Treatment

# The MARS® circuit



**MARS®FLUX DIALYZER**    **diaMARS®ADSORPTION COLUMNS**    **diaFLUX DIALYZER**



PATIENT

BLOOD CIRCUIT

MARS®ALBUMIN CIRCUIT

DIALYSATE CIRCUIT

# **Effects of MARS® in Acute on Chronic Hepatic Failure**

(Review of reported effect)

## **Hemodynamic**

**Increased Mean arterial Pressure (MAP)**  
**Decrease cardiac output**  
**Increased Vascular systemic resistance**  
**Decrease in NO**

## **Renal**

**Decrease Renin**  
**Decrease Aldosterone**  
**Decrease Norepinephrine**  
**Increased Atrial natriuretic peptide**

## **Hepatic**

**Increased Hepatic Blood flow (HBF)**  
**Increased Hepatic delivery of O<sub>2</sub> (HDO<sub>2</sub>)**  
**No change in Hepatic venous oxygen consumption (HvO<sub>2</sub>)**  
**Decrease of Portal Pressure**

# MARS® in the treatment of Acute alcoholic hepatitis

- 8 patients with severe AAH (jaundice, encephalopathy or renal impairment)
  - mean Maddrey score: 69 and (HVGP >12 mmHg)
- 1 session of MARS (6 h).
- 3 patients received 1 session of hemodialysis (control group, non randomised).

## Results

- **At the end of MARS session (H6), mean HVGP decreased from 17 to 11 mm Hg (p= 0.003).**
- **Reduction was maintained 24h without a rebound effect.**
- **A reduction  $\geq$  20% was noted in 7/8 patients.**
- **6/7 patients reduced their HVGP < 12 mmHg.**
- **A significant increase in mAP : 72 to 80 mm Hg.**
- Hemodialysis alone didn't have any effect on HVGP and mAP

# MARS efficiency: Bio-chemical and clinical data before and after treatments

Meta Analysis of 149 HBV patients from 14 centers in China

ALF (11%), SALD (8%), AoCLD (81%); Average MARS treatment: 2.33/patient

Parameters	No. of patients	Pre-MARS	Post-MARS
TB ( $\mu\text{mol/L}$ )	149	332.4 $\pm$ 97.2	218.6 $\pm$ 78.7**
PTA (%)	149	31.7 $\pm$ 14.0	38.7 $\pm$ 13.1*
Creatinine ( $\mu\text{mol/L}$ )	92	235.7 $\pm$ 110.3	163.2 $\pm$ 77.6*
BUN (mmol/L)	92	9.8 $\pm$ 2.6	4.9 $\pm$ 2.3**
S-sodium (mmol/L)	92	140.8 $\pm$ 5.2	145.3 $\pm$ 3.9*
Ammonia (mmol/L)	117	121.4 $\pm$ 6.9	89.7 $\pm$ 5.4**
NO ( $\mu\text{mol/L}$ )	30	44.2 $\pm$ 17.8	29.9 $\pm$ 16.7*
TNF- $\alpha$ (pg/ml)	43	2.70 $\pm$ 1.8	1.99 $\pm$ 1.29*
IL-6 ( $\mu\text{mol/L}$ )	24	41.1 $\pm$ 19.7	26.3 $\pm$ 18.9*
IL-8 (pg/ml)	24	101.8 $\pm$ 98.2	79.9 $\pm$ 53.7*
MAP (mmHg)	87	75.1 $\pm$ 8.3	81.8 $\pm$ 6.9*
CTP (point)	98	10.3 $\pm$ 2.3	8.2 $\pm$ 2.0*
HE (grade)	98	2.9 $\pm$ 1.2	1.5 $\pm$ 1.1*

\* $P < 0.05$ , \*\* $P < 0.01$  compared with Pre-MARS.

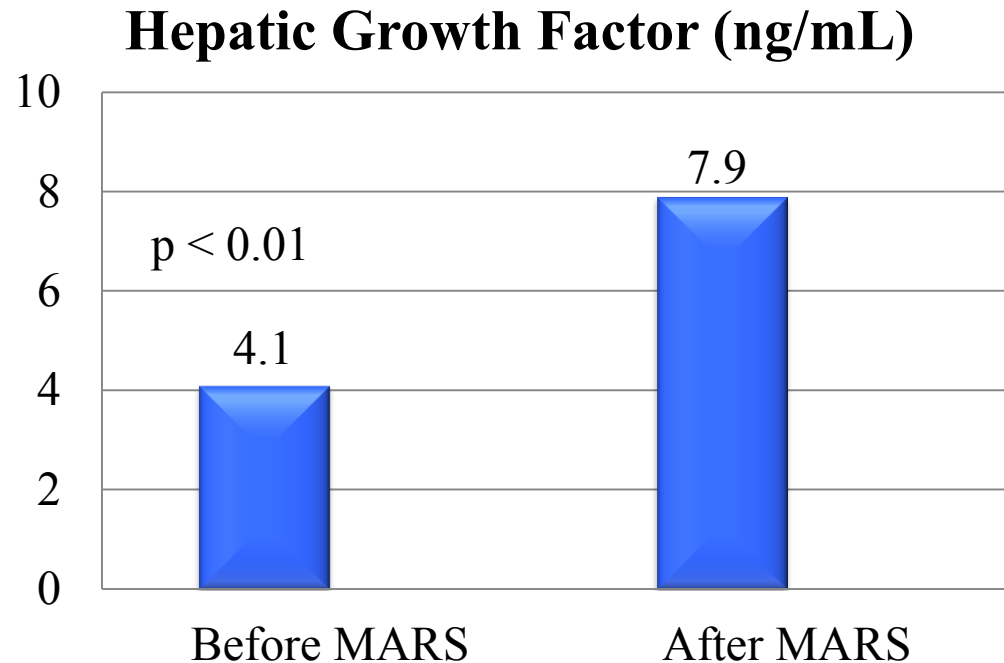
# **Extracorporeal Detoxification for Hepatic Failure Using MARS: Depurative Efficiency and Clinical Results in a Long-Term Follow-Up**

**64 patients with life-threatening liver failure - 269 MARS treatments**

- **Reduction rate per session was for:**
  - Total bilirubin : 23% (range 17-29)
  - Direct bilirubin RRs : 28% (21-35)
  - Indirect bilirubin RRs : 8% (3-21).
  - Ammonia RRs : 34% (12-86).
  - Conjugated cholic acid RRs : 58% (48-61);
  - Chenodeoxycholic acid RRs : 34% (18-48).

# Extracorporeal Detoxification for Hepatic Failure Using MARS: Depurative Efficiency and Clinical Results

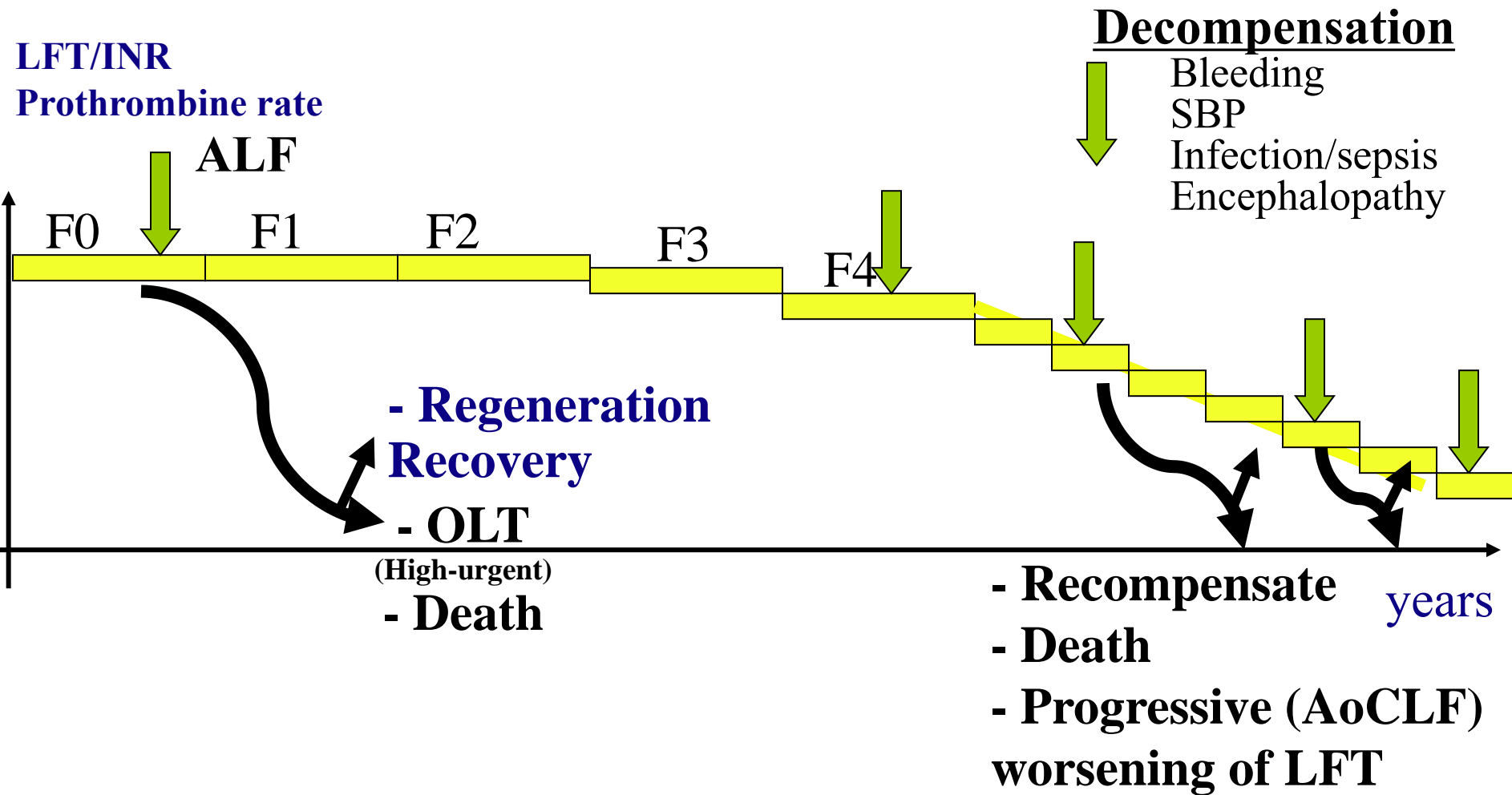
64 patients with life-threatening liver failure - 269 MARS treatments



Risk factors predicting patient outcomes (Cox regression analysis)

- age, male gender, and SOFA score were factors predicting death
- the number of MARS sessions and the  $\Delta$ HGF proved protective factors

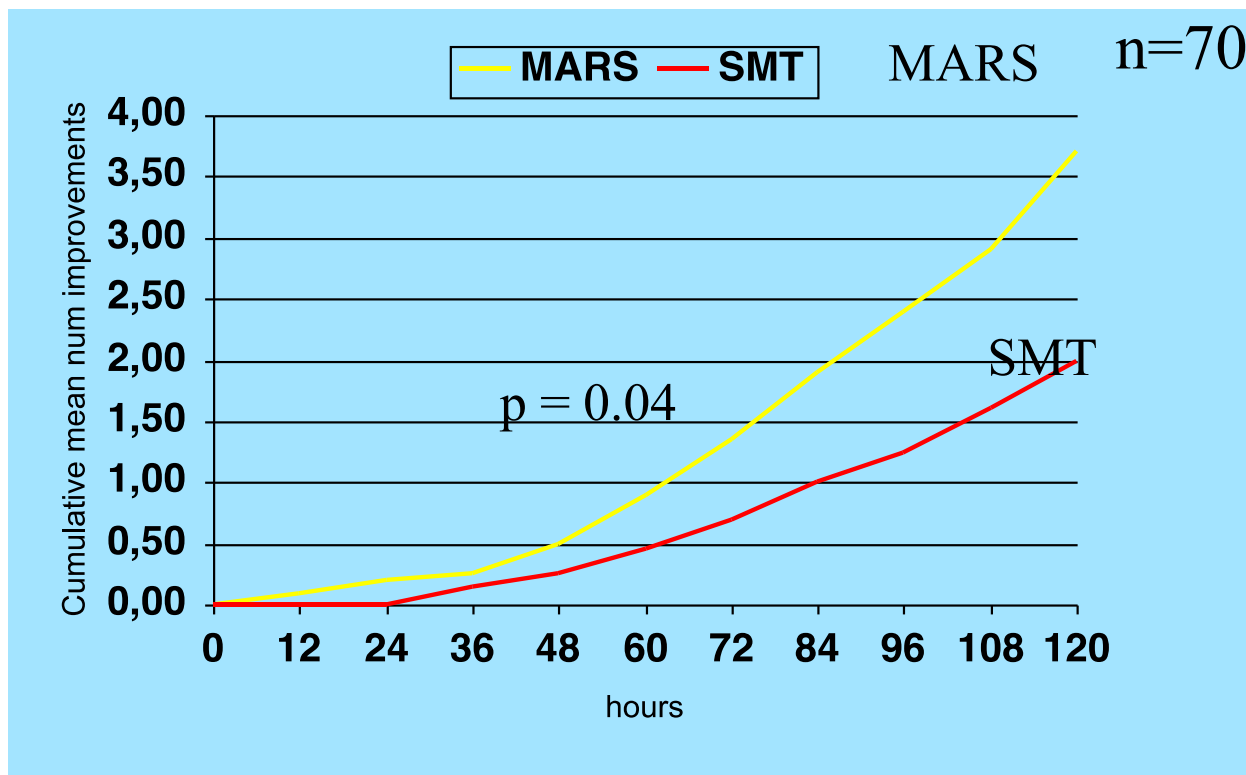
# Potential of Regeneration according to the progression of the disease



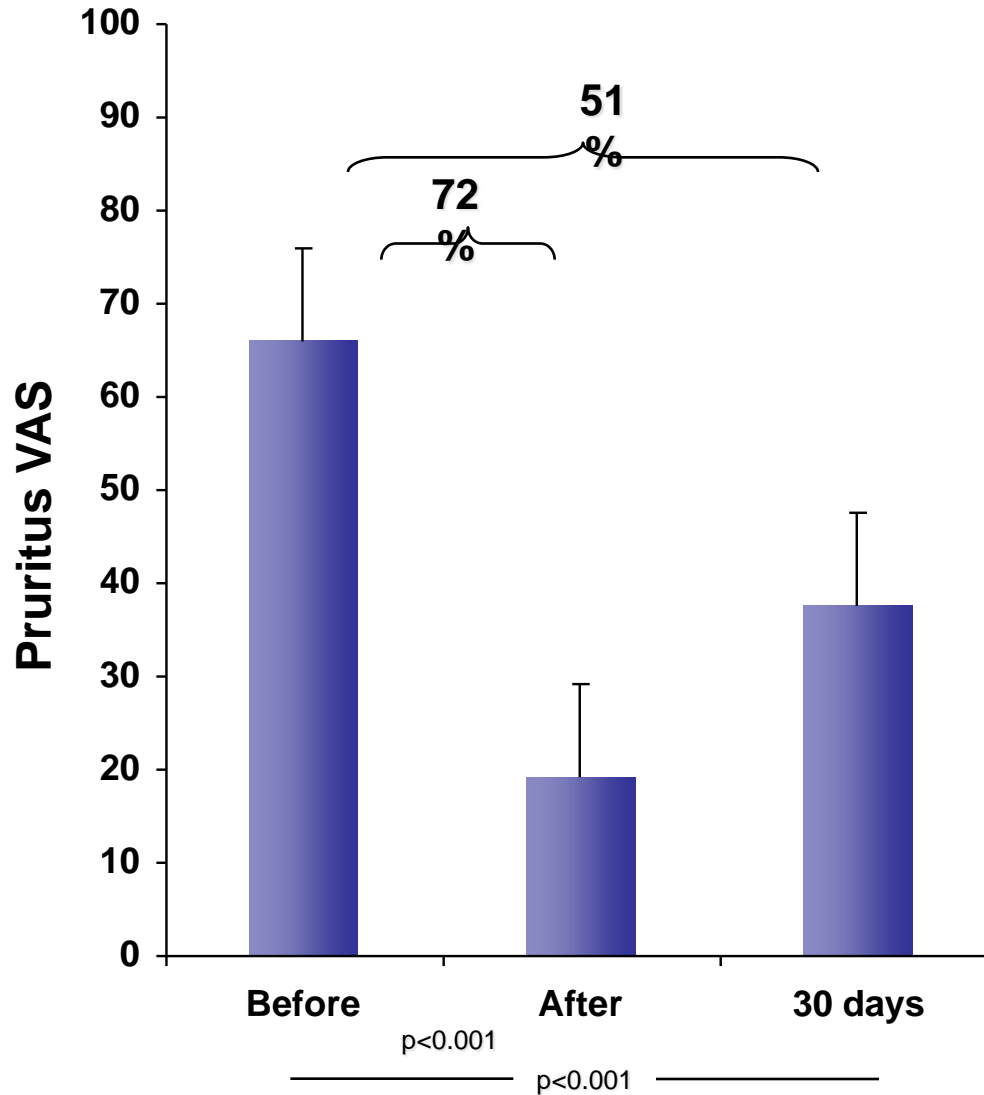
# Efficacy of MARS® in patients with hepatic encephalopathy (HE) grade III et IV

A prospective controlled randomised multicenter study 70 pts  
SMT vs SMT+MARS x maximum 5 days

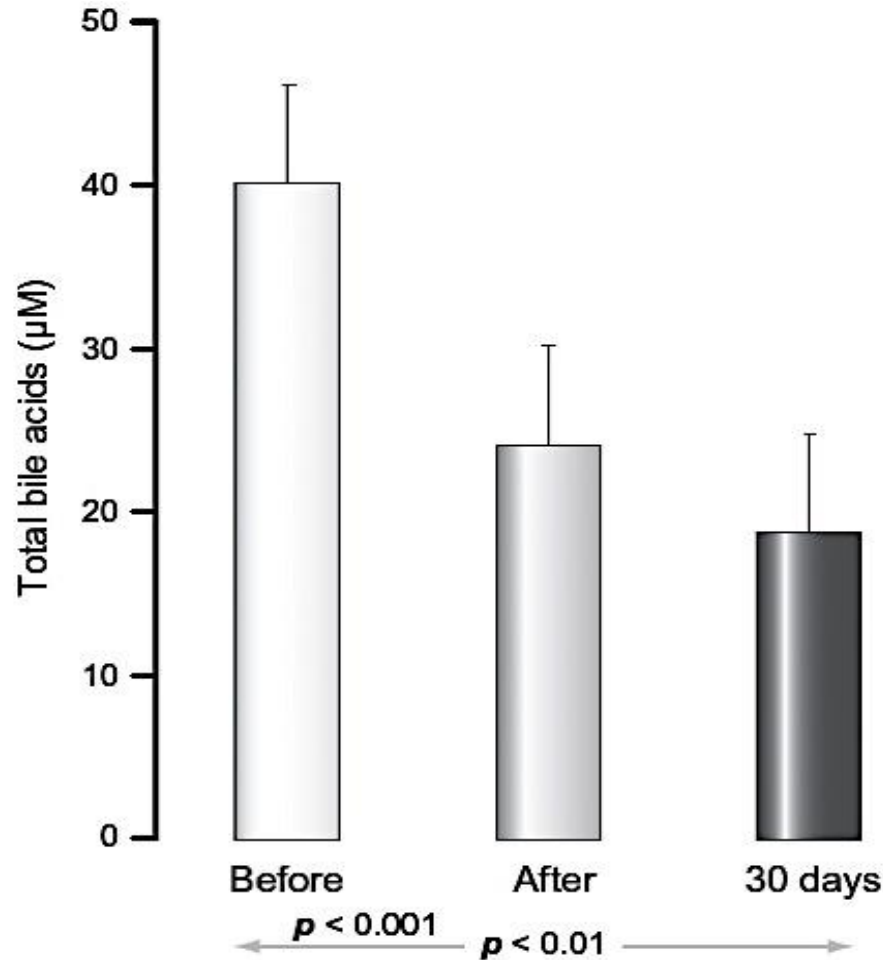
- Improvement of HE 64% (MARS®) vs 38% (SMT®)
- Median Time to improvement 60 h vs 102 h



# Effect of MARS on pruritus



# Circulating bile acid concentration in patients with pruritus before and after treatment with MARS®



# The RELIEF trial:

Recompensation of Exacerbated Liver Insufficiency with Hyperbilirubinaemia and/ or Encephalopathy and/or renal Failure

- Multicenter prospective randomized trial: SMT vs. SMT + MARS
- Main end-point : 28 days transplant-free survival
- **Inclusion criteria:**
  - Acutely decompensated liver cirrhosis
  - Bilirubin >5 mg/dl (without evidence of extrahepatic origin)AND... at least one of:
  - HRS (International Ascites Club) and/or
  - Hepatic encephalopathy  $\geq$  II and/or
  - Progressive hyperbilirubinemia (Bilirubin > 20 mg/dl)
- **Main exclusion criteria**
  - Platelet count less than 50000/mm<sup>3</sup>
  - INR >2.3 or DIC
  - Need for renal replacement or intrinsic renal disease
  - Uncontrolled infection

# Baseline characteristics (PP population)

Variable	SMT (n=85)	SMT+ MARS (n=71)	P
Age (years)	50 (11)	51.8 (10.4)	NS
Sex (male (%))	61 (71.8 %)	46 (64.8 %)	NS
Etiology of liver disease*			NS
Alcohol	80 (94.1 %)	64 (90.1 %)	
Viral hepatitis	7 (8.2 %)	5 (7 %)	
Others	6 (7.1 %)	9 (12.6 %)	
Alcohol abuse (n (%))	66 (77.6 %)	55 (77.5 %)	NS
Infection (n (%))	26 (30.6 %)	20 (28.2 %)	NS
GI Bleeding (n (%))	12 (14.1 %)	8 (11.3 %)	NS
Dehydration (n (%))	8 (9.4 %)	6 (8.5 %)	NS
Others (n (%))	5 (5.9 %)	1 (1.4 %)	NS
More than one precipitating event (n (%))	32 (37.6 %)	29 (40.8 %)	NS
Number of precipitating events (median (range))	1 (1-4)	1 (1-3)	NS
<b>SBP (n (%))</b>	<b>6 (7.1 %)</b>	<b>12 (16.9 %)</b>	<b>P=0.055</b>

*\*more than one cause is possible*

# Baseline characteristics (PP population)

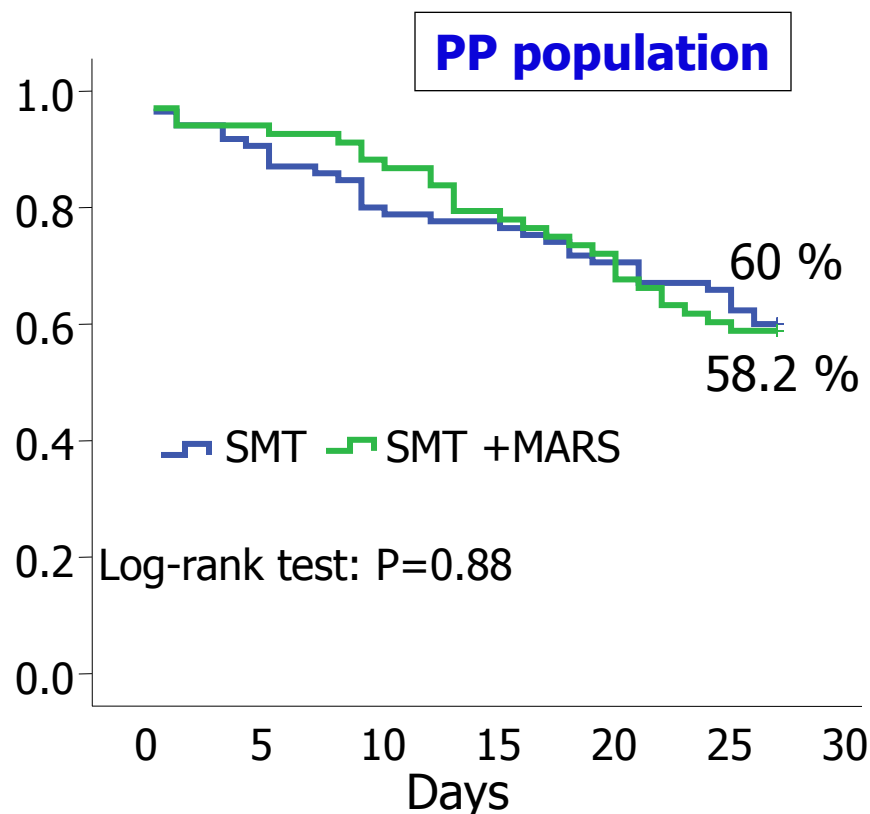
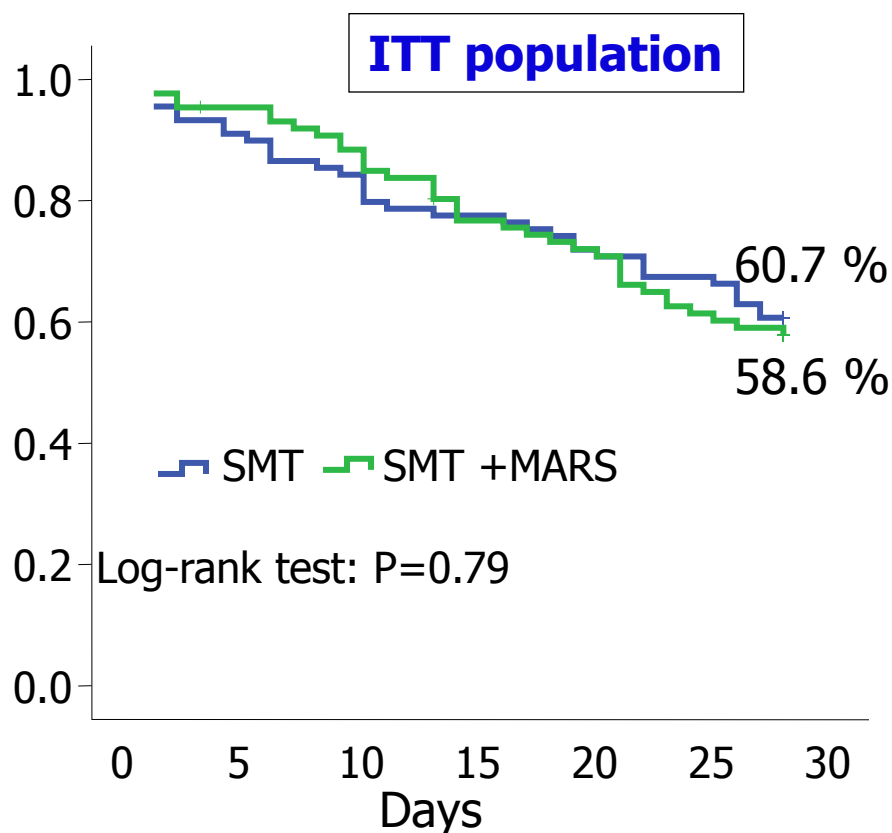
Variable	SMT (n=85)	SMT+MARS (n=71)	P
Progressive hyperbilirubinemia (n (%))	60 (70.6 %)	46 (64.8 %)	NS
HRS (n (%))	45 (52.9 %)	37 (52.1 %)	NS
Encephalopathy $\geq$ grade II (n (%))	37 (43.5 %)	28 (39.4 %)	NS
SOFA score (n=95)	7.7 (3.3)	8.1 (2.8)	NS
Glasgow (n=140)	13.05 (3.23)	13.06 (3.61)	NS
Bilirubin (mg/dl)	27.0 (12.3)	26.8 (11.8)	NS
Albumin (g/L)	28.1 (9.9)	27.3 (6.3)	NS
Serum creatinine	2.27 (2.07)	2.50 (2.20)	NS
INR	1.78 (0.33)	1.74 (0.31)	NS
Hematocrit	29.3 (6.0)	28.4 (4.8)	NS
Leucocytes	15.6 (11.0)	16 (9.6)	NS
Platelet count	120.3 (72.3)	130.9 (75.2)	NS
<b>MELD &gt; 20 (n(%))</b>	<b>59 (69.4 %)</b>	<b>58 (81.7 %)</b>	<b>P=0.078</b>

# MARS in patients with acute-on-chronic liver failure

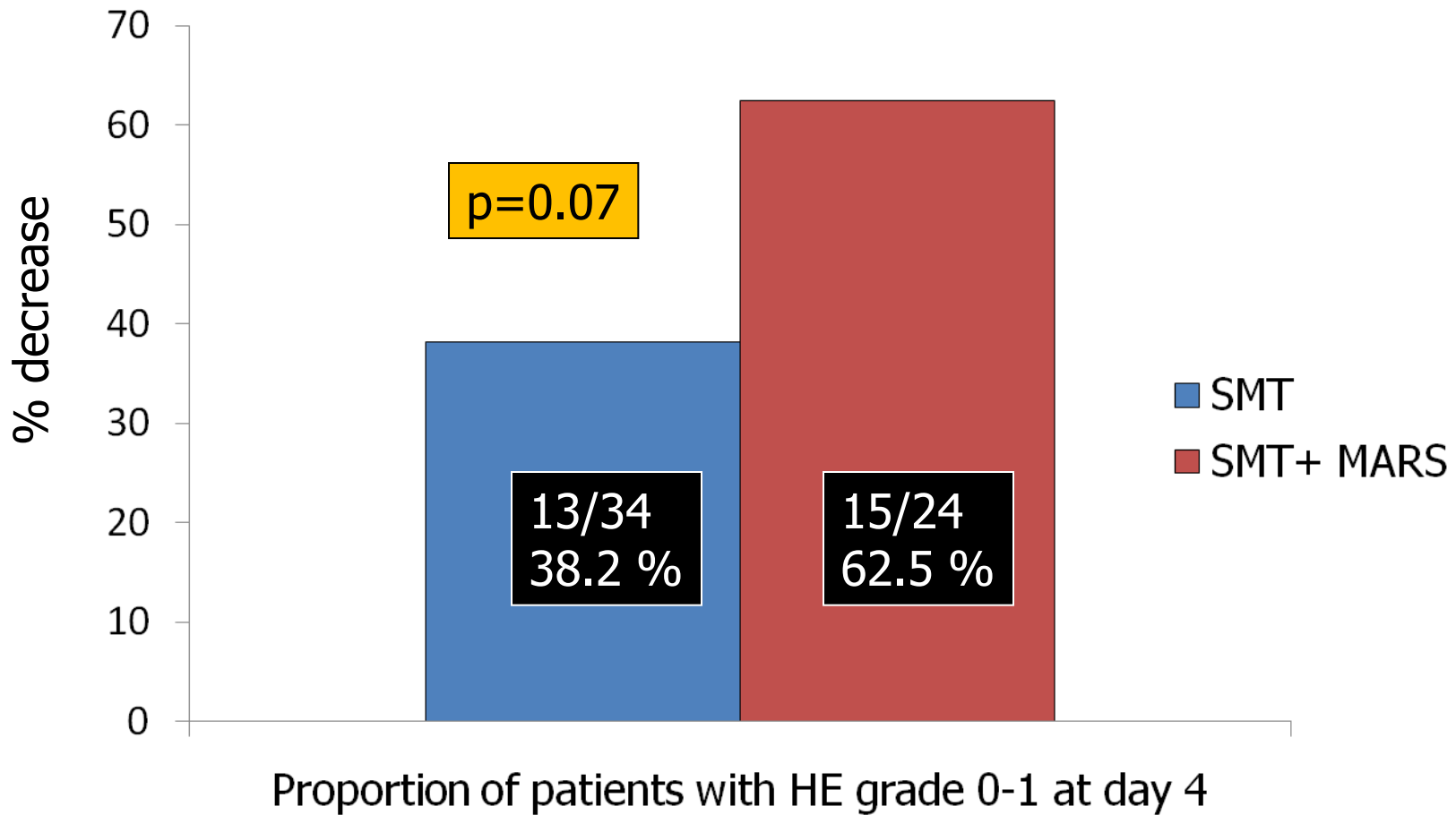
## The RELIEF Trial

A multicenter randomized controlled trial SMT vs SMT + MARS

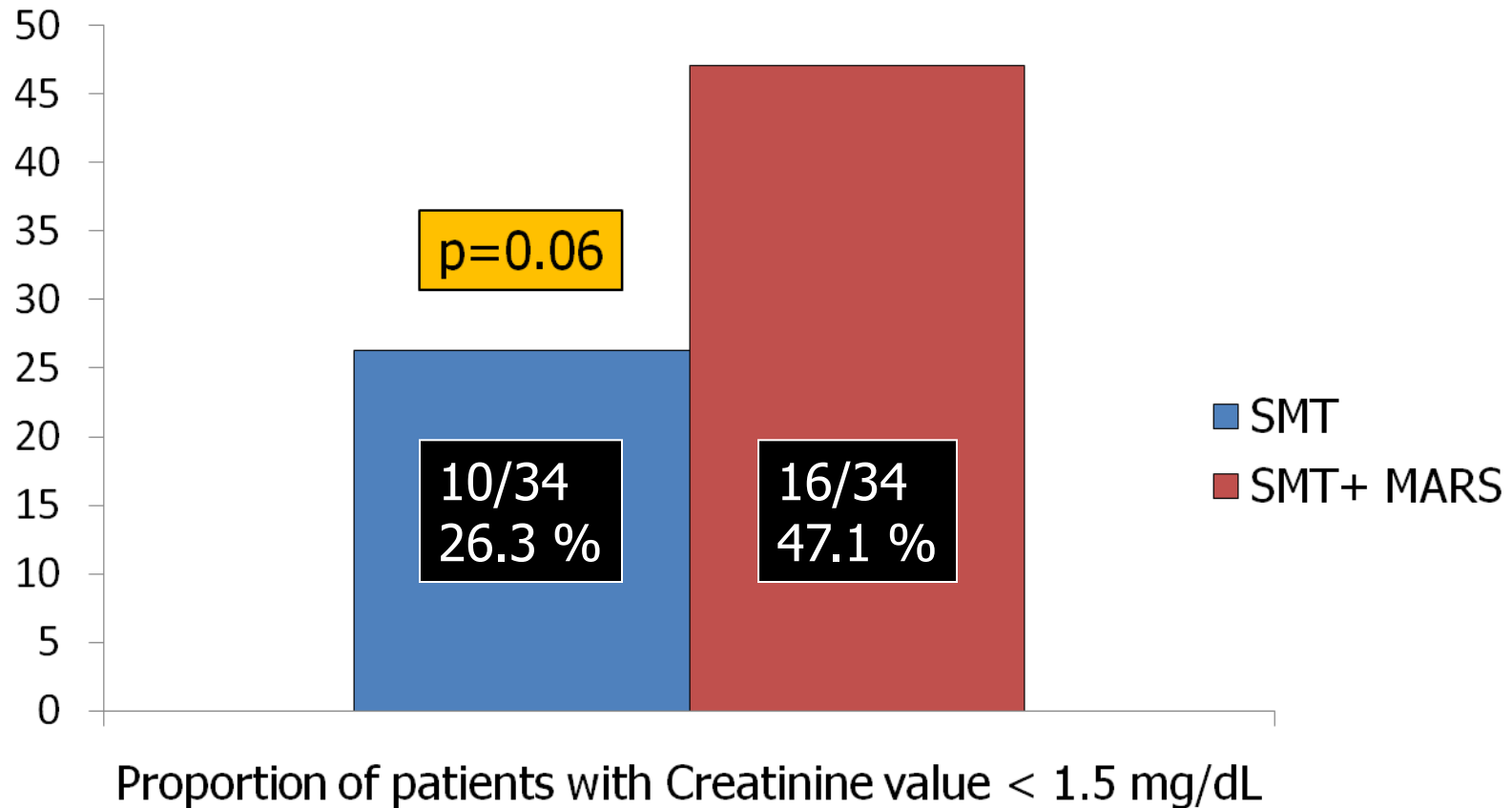
Primary endpoint: 28 days transplant-free survival



# Effects on Hepatic Encephalopathy (PP population) at day 4; n=58



# Effects on renal function in patients with HRS (PP population) at day 4; n=72



# HELIOS study

## Prometh<sup>h</sup>eus<sup>®</sup> European Liver Disease Outcome Study

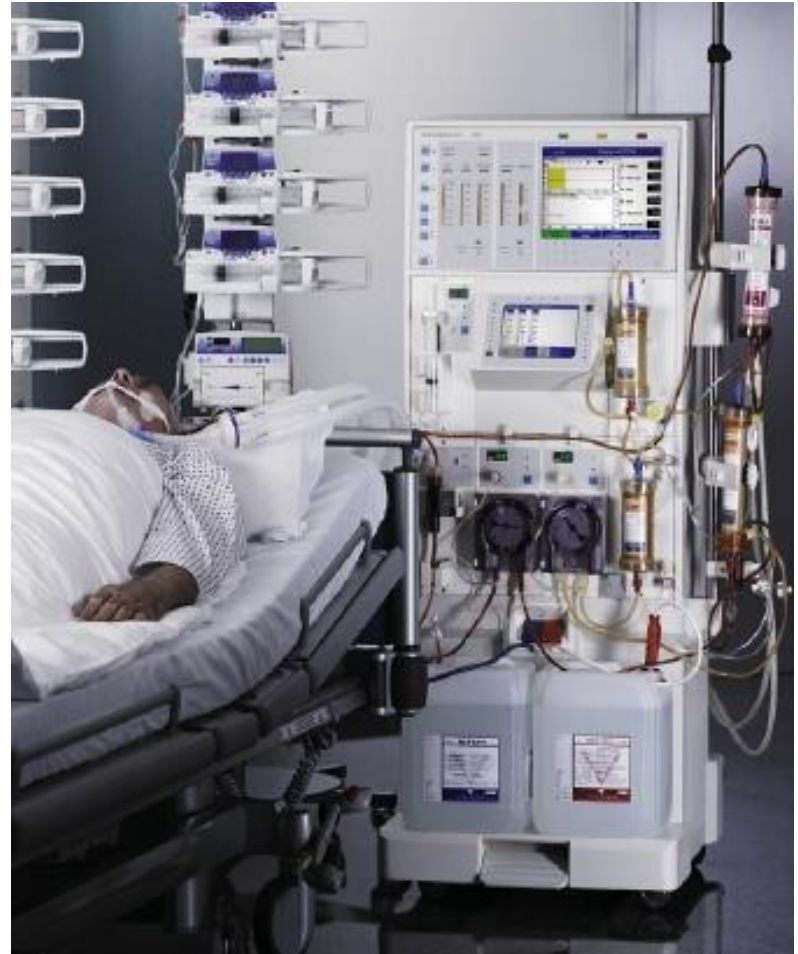
### Objective:

- To test survival under Prometheus therapy with standard medical therapy (SMT) *compared to* SMT alone

### Patients:

- Acute decompensation of chronic liver disease
- Presence within last 72 hours of
  - CP-Score  $\geq 10$
  - Bilirubin  $\geq 5$  mg/dl
- Exclusion: 16 major comorbidities

Kribben A et al, *Gastroenterology* 2012;142(4):782-789



# Helios Study design

## 1. Screening phase

3 days



**Randomisation**

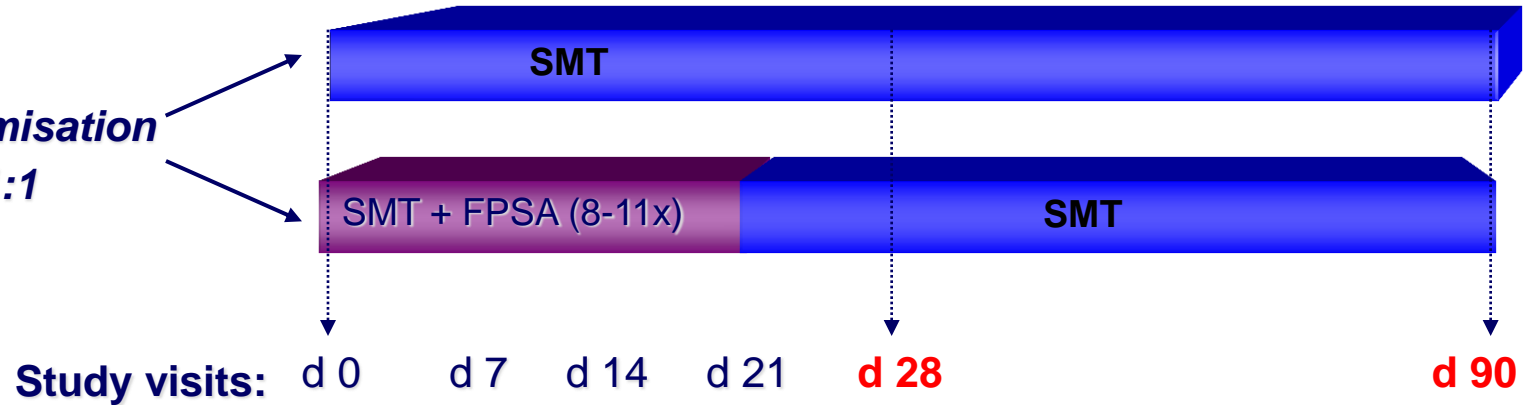
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## 2. Treatment phase

21 days

## 3. Follow up phase

69 days



1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21							
5 treatm. in 7 days							3 treatm. during the first 5 days							3 treatm. in the 1 <sup>st</sup> 5 days (if needed)													
1 <sup>st</sup> therapy block mandatory							2 <sup>nd</sup> therapy block mandatory							3 <sup>rd</sup> therapy block according to protocol													
●							●					●							●								
							8±1							13±1							20±1						

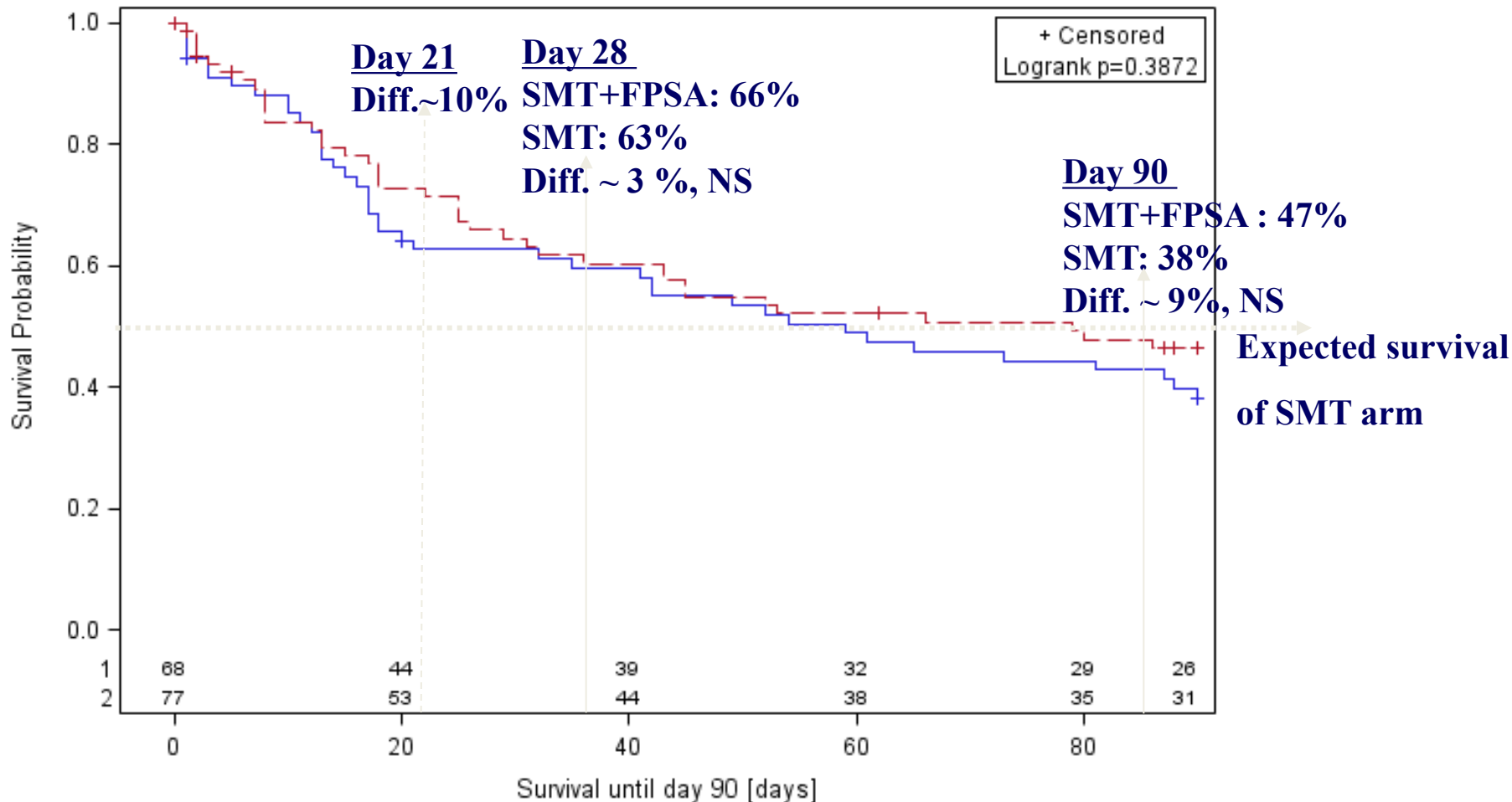
Start of study

8-11 treatments of each at least 4 hours duration

# Baseline data

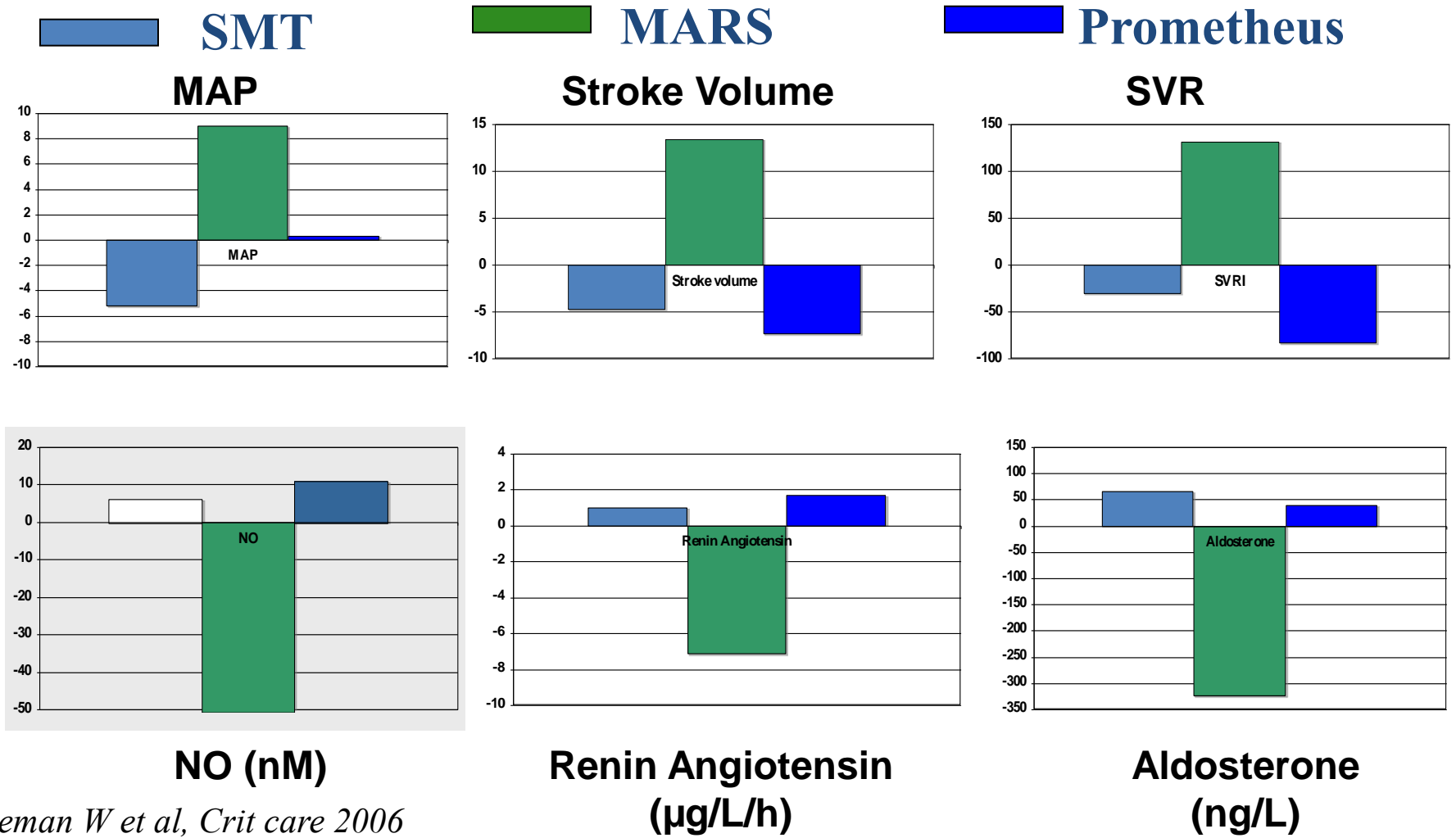
	SMT n = 68	SMT+FPSA n = 77		SMT n = 68	SMT+FPSA n = 77
Age (years)	51 ± 9	50 ± 11	Hepatic encephalopathy any grade, n (%)	56 (82)	59 (77)
Sex (male %)	65	62	HE grade 1, n (%)	37 (54)	39 (51)
Alcoholic liver disease, n (%)	44 (65)	37 (48)	Acute renal failure, n (%)	38 (56)	42 (55)
Viral liver disease, n (%)	14 (21)	15 (20)	HRS type 1, n (%)	18 (26)	27 (35)
Alcoholic and viral liver disease, n (%)	2 (3)	8 (10)	Spontaneous bacterial peritonitis, n (%)	16 (24)	14 (18)
Other etiology of liver disease, n (%)	8 (12)	17 (22)	Assisted respiration, n (%)	10 (14)	6 (8)
Time since precipitating event (days)	14.5 ± 12.1	17.5 ± 31.6	Bilirubin (mg/dl)	25 ± 14	26 ± 15
Time since hospital admission (days)	12.5 ± 10.9	11.1 ± 11.4	Albumin (g/dl)	2.9 ± 0.5	3.0 ± 0.6
Child Pugh score	12 ± 1	12 ± 1	INR	1.98 ± 0.56	2.00 ± 0.42
MELD score	27 ± 10	28 ± 10	Serum sodium (mmol/l)	135 ± 7	135 ± 6
SOFA score	10 ± 4	10 ± 3	Serum creatinine (mg/dl)	2.3 ± 2.0	2.3 ± 2.0
Ascites, n (%)	66 (97)	70 (91)	Listed for OLT at baseline, n (%)	13 (19)	17 (22)

# PROMETHEUS in patients with acute-on-chronic liver failure : The HELIOS Trial (RCT)



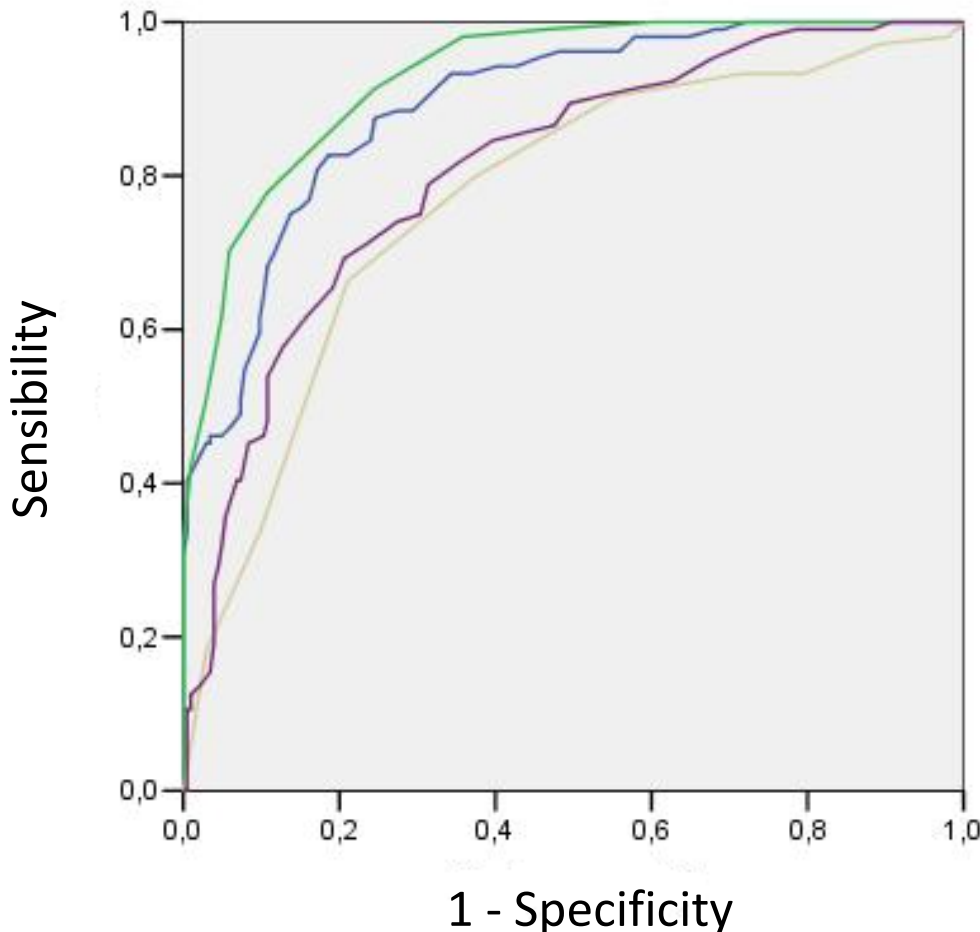
# Comparative studies MARS® vs Prometheus Haemodynamics comparison

- 18 pts, AAH/alcoholic cirrhosis, Child-Pugh 12.5, Maddrey score 63 + 5
- 6 MARS®, 6 Prometheus®, 6 SMT



# Cirrhotic patients admitted to the ICU Prognostic Scores (AUC-ROC)

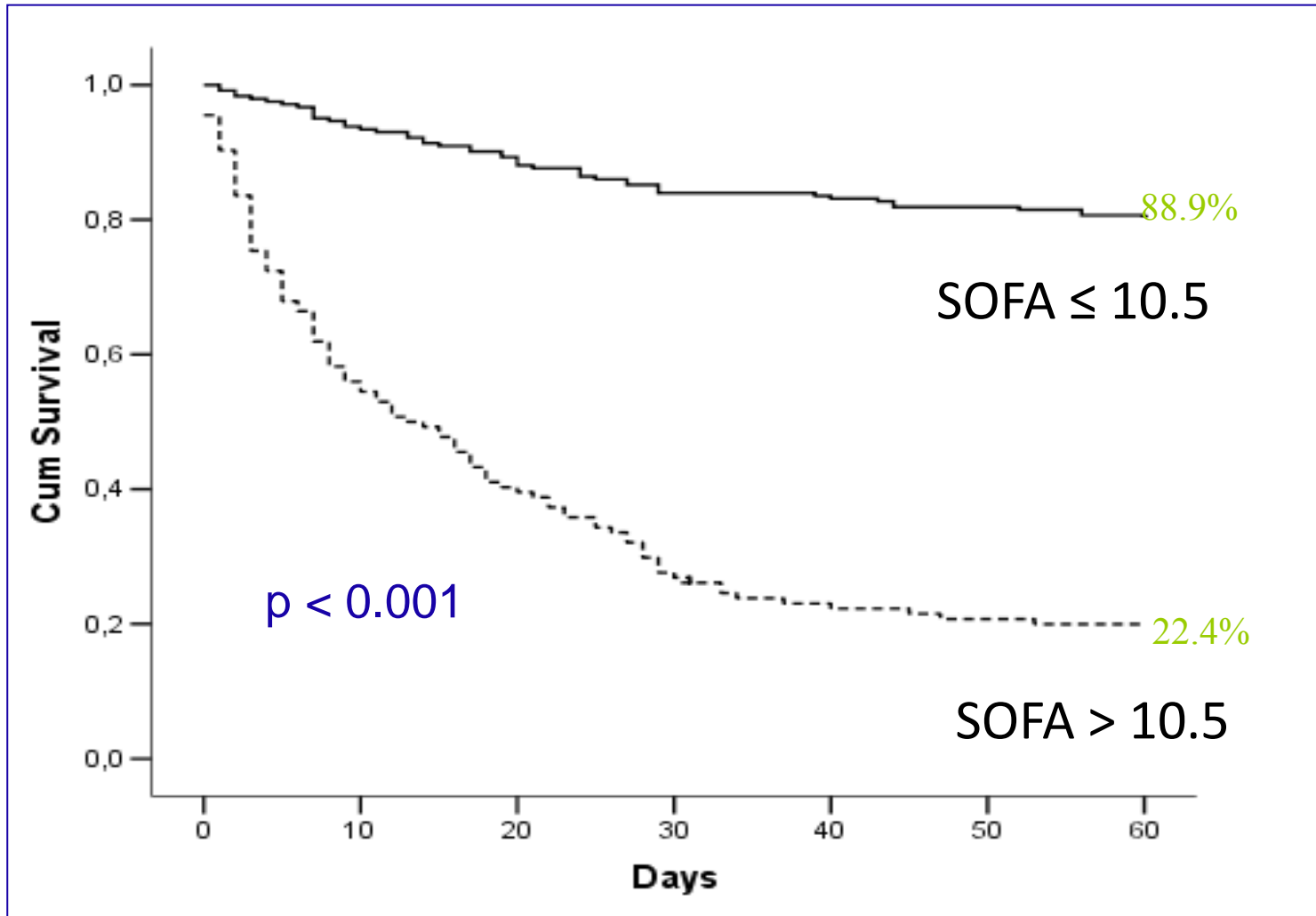
All population n=377



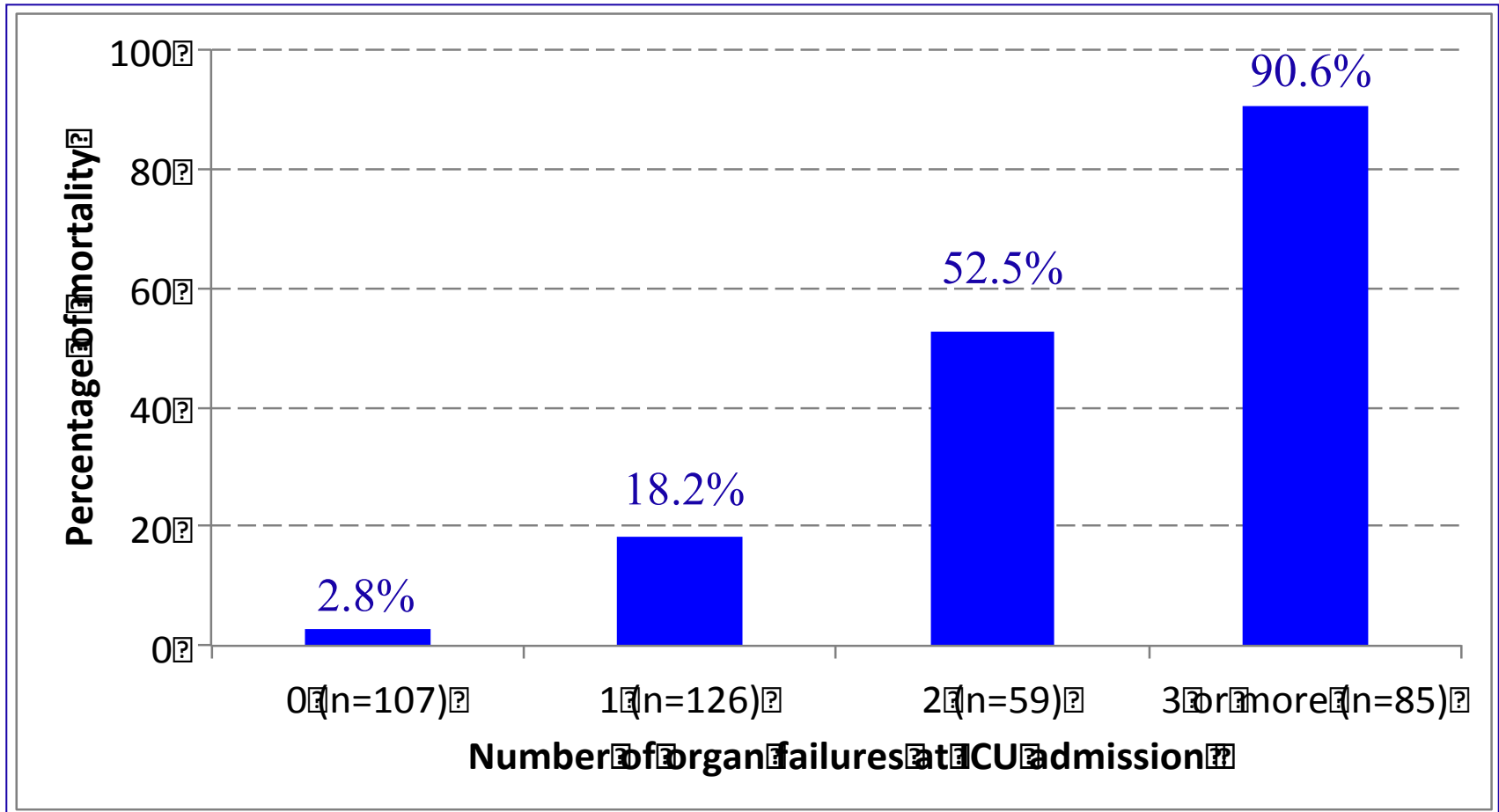
— SOFA  
— SAPS II  
— MELD  
— Child Pugh

Test	AUC
SOFA	0.92
SAPS II	0.89
MELD score	0.82
Child Pugh	0.79

# Survival (2 months) by SOFA score



# Mortality rate by Organ failure defined by a SOFA score $\geq 3$



# ICU/Hospital mortality according to number of organ failure

**Table 2.** ICU/Hospital mortality according to number of organ failure in critically-ill cirrhotic patients

<b>Authors(year) [Ref.]</b>	<b>No organ failure</b>	<b>1 organ failure</b>	<b>2 organs failure</b>	<b>≥ 3 organs failure</b>
Jalan et al (2012)** [22]	1.9% / 10%	23% / 41%	31% / 55%	74% / 78%
Levesque et al (2011) [9]	2.2 %	5.8 %	77.9 %	96.1 %
Das et al (2010)* [8]	12 % / 23 %	49 % / 54 %	64 % / 67%	71% / 89 %
Gildea et al (2004) [17]	11%	42%	66%	92%
Wehler et al( 2001) [18]	6.4%	33.3%	73.3%	96.7%
Aggarwal et al (2001) [23]	1.1%	18%	50%	83.7%

\* Mortality according to presence of organ failure respectively at day 1 and day 3

\*\* Mortality rates respectively at day 28 and day 90.

# The CANONIC Study

## Acute on Chronic liver Failure in Cirrhosis

- EASL-CLIF (Chronic Liver Failure) Consortium Group
- 2149 consecutive patients prospectively evaluated in 29 European hospitals.
- **Enrolment:** From Feb 1 to Aug 15, 2011.
- **Inclusion criteria**
  - Patients with cirrhosis admitted to hospital for more than one day for the treatment of a complication of liver disease.
- **Main exclusion criteria**
  - Patients admitted for scheduled procedures.
  - Decompensation following partial hepatectomy.
  - HCC outside Milan criteria.
  - Severe chronic extrahepatic disease.

# The CANONIC Study

## Acute on Chronic Liver Failure in Cirrhosis

### GENERAL AIMS

- To investigate pathophysiology, precipitating events, clinical course and outcome of acute-on-chronic liver failure in patients with cirrhosis admitted to the hospital for a complication of liver disease.

### SPECIFIC AIMS

- To understand molecular mechanisms of acute-on-chronic liver failure
- To elaborate diagnostic criteria that may be applicable in clinical practice
- To identify patients who are at risk of developing acute-on-chronic liver failure in whom preventive interventions should be developed
- To elaborate a prognostic index able to accurately assess 28-day mortality
- To identify biomarkers for acute-on-chronic liver failure

# Definition of organ failure

## Modified SOFA score for Cirrhosis (The CLIF-SOFA SCORE)

Organ/system	0	1	2	3	4
<b>Liver</b> (Bilirubin, mg/dL)	<1.2	≥1.2 - ≤1.9	≥2 - ≤5.9	≥6 - <12	≥12
<b>*Kidney</b> (Creatinine (mg/dL))	<1.2	≥1.2 - ≤ 1.9	≥2 - <3.5                      ≥3.5 - <5                      ≥5 or use of renal-replacement therapy		
<b>*Cerebral</b> (HE grade)	No HE	1	2	3	4
<b>*Coagulation (INR)</b>	<1.1	≥1.1 – <1.25	≥1.25 - <1.5	≥1.5 – <2.5	≥2.5 or Platelets ≤20x10 <sup>9</sup> /L
<b>*Circulation</b> (MAP mm Hg)	≥70	<70	Dopamine ≤5 or Dobutamine or Terlipressin	Dopamine >5 or E ≤ 0.1 or NE ≤ 0.1	Dopamine >15 or E > 0.1 or NE > 0.1
<b>Lungs</b> <b>PaO<sub>2</sub>/FiO<sub>2</sub>:</b> <b>or</b> <b>SpO<sub>2</sub>/FiO<sub>2</sub></b>	>400  >512	>300 - ≤400  >357 - ≤512	>200 - ≤300  >214 - ≤357	>100 - ≤200  >8 - ≤214	≤100  ≤89

\*modifications to SOFA score

# Organ failure is associated with high 28-day mortality

PREVALENCE

MORTALITY

**Organ failure**

**32.9%**

**26.9%**

**No Organ failure**

**67.1%**

**4.4%**

1 Organ failure

21.4%

14.6%

2 Organ failures

8.0%

32.0%

3 Organ failures

2.1%

68.0%

> 3 Organ failures

1.4%

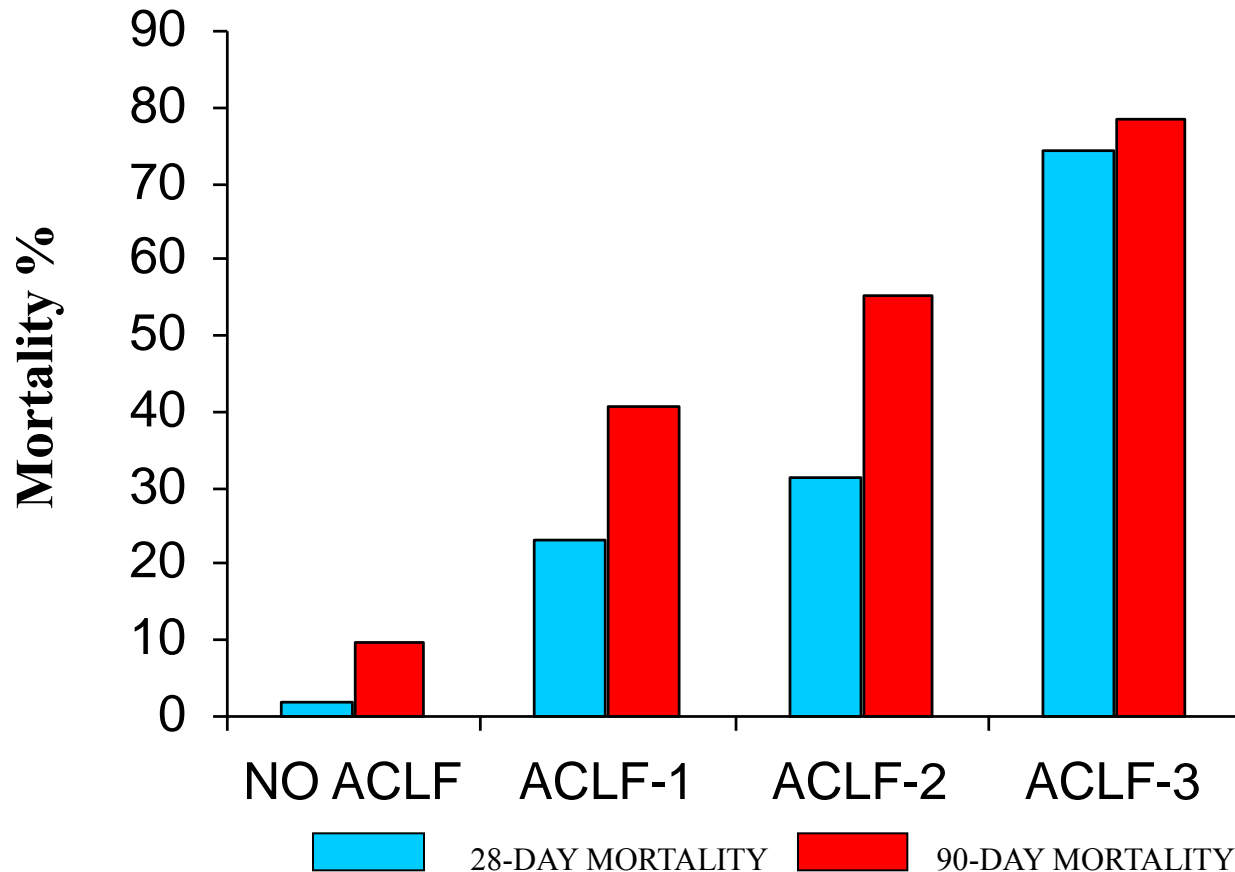
88.9%

# Diagnostic criteria and grades of ACLF

- **No ACLF**
  - Patients with no organ failure
  - Patients with single hepatic, coagulation, circulation or respiratory failure, serum creatinine <1.5 and no HE
  - Patient with cerebral failure and serum creatinine <1.5
- **ACLF 1**
  - Patients with renal failure
  - Patients with other single organ failure with serum creatinine  $\geq 1.5$  mg and <2; and/or HE grade 1-2.
- **ACLF 2**
  - Patients with 2 organ failures
- **ACLF 3**
  - Patients with 3 or more organ failures

# CANONIC Study : 1343 patients, 29 Centres

## 28-day and 90-day mortality in ACLF



- The prevalence of ACLF in patients with AD is 30%
- ACLF is especially severe in patients without a prior history of AD.

# Prognosis in cirrhotics by need for organ support during ICU hospital stay

One organ support alone	Ventilation	Noradrenaline	Hemodialysis*	MARS®
N° of patients	29	8	2	13
Survival (n)	27	8	2	12
Survival (%)	93.1%	100%	100%	92.3%

Two organs support	Ventilation + Noradrenaline	Ventilation + Hemodialysis	Ventilation + MARS®	Noradrenaline + Hemodialysis / MARS®
N° of patients	89	0	1	5
Survival (n)	15	-	1	5
Survival (%)	16.9%	-	100%	100%

# Prognosis in cirrhotics by need for organ support during ICU hospital stay

Three organs support	Ventilation + Noradrenaline + Hemodialysis*	Ventilation + Noradrenaline + MARS®
N° of patients	34	16
Survival (n)	1	1
Survival (%)	2.9%	6.2%

\* CVVHDF

# Conclusion

- Même si les données actuelles sont peu contributives sur le réel bénéfice du MARS sur la survie des patients, Le MARS permet :
  - Une amélioration de l'état clinique
  - Une amélioration de l'état hémodynamique pour certains patients
  - Une amélioration de l'encéphalopathie hépatique
  - Une amélioration du syndrome hépato-rénal
  - Un traitement d'attente pour une transplantation hépatique
- Un grand besoin d'homogénéisation et d'évaluation des patients dans cette indication
- L'évaluation devrait se faire en fonction :
  - des scores de gravités de réanimation : MELD, SOFA, CLIF-SOFA
  - du nombre de défaillance d'organes et de suppléances thérapeutiques
  - de la présence ou non de SIRS ou Sepsis

# Albumin dialysis with MARS®

## An International Registry

*Livernet® is an interactive observational registry that enables any center or physician worldwide to register all patients treated with MARS ©*

### *Main objectives:*

- *Current insight on the indications and technical aspects of MARS®*
- *Efficacy and safety of the system in specific indications.*

# Avantages de la base [www.livernet.net](http://www.livernet.net)

- **CRF électronique en ligne innovant avec comme avantages :**
  1. Facilité et une rapidité au niveau de la saisie de données
  2. “Queries” instantannées avec 3 niveaux d’importance
  3. Chaque centre est propriétaire de ses données :
    - Export direct et instantané vers une base de données fichier excel que dispose chaque centre pour ses propres données
  4. Statistiques directes instantannées en ligne (exportables) par centre et pour l’ensemble des centres
  5. Statistiques complètes annuelles de la base