Decompensated Cirrhosis End Points: ACLF and MELD

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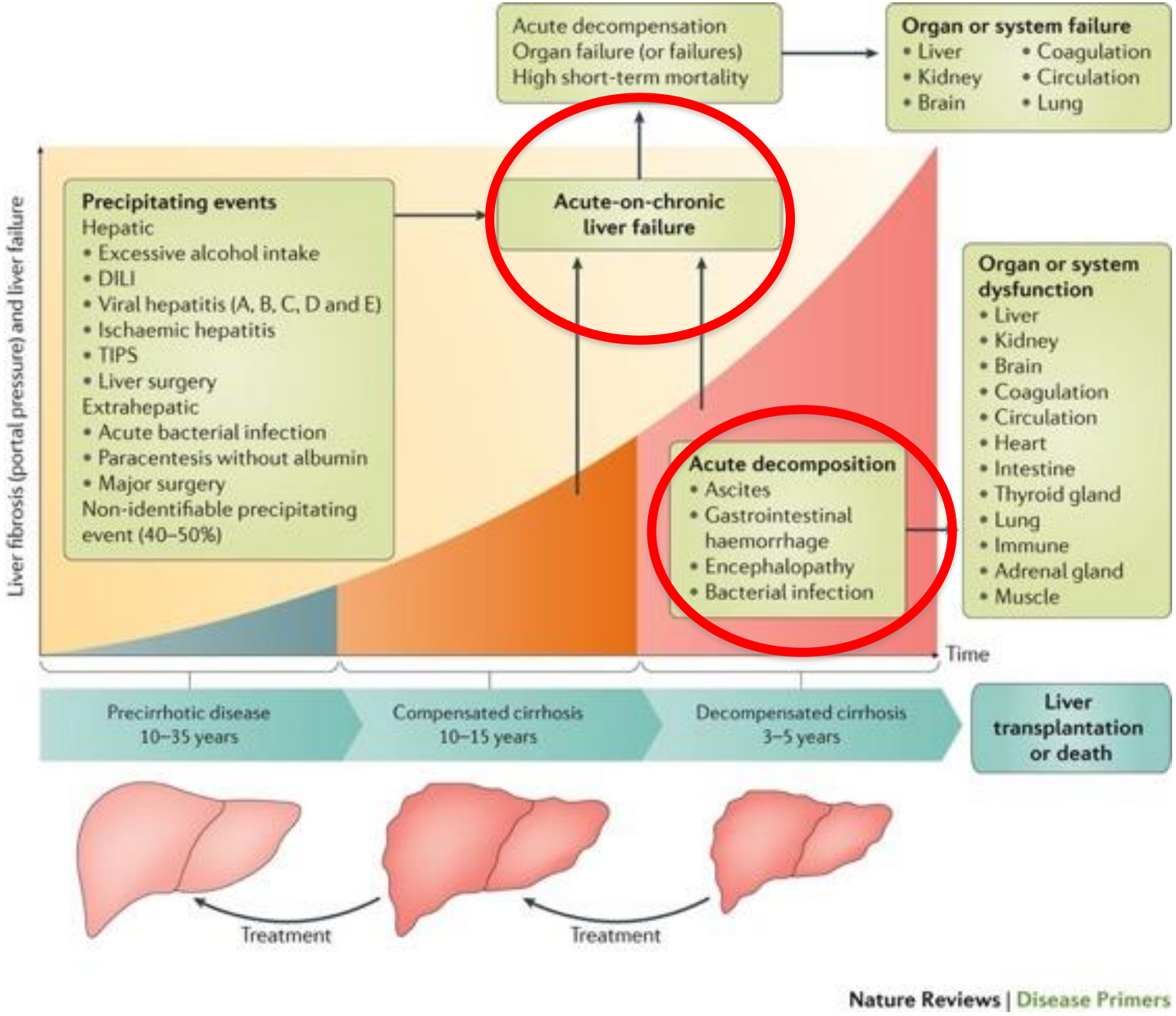
Disclosures:

- **Inventor:** Ornithine phenyl acetate for the treatment of hepatic encephalopathy (licensed to Ocera Therapeutics)
- **Research Collaboration:** Ocera Therapeutics, Yaqrit limited
- **Founder:** UCL spin-out company, Yaqrit Ltd
  - Yaq-001
  - DIALIVE
  - TLR4 antagonist

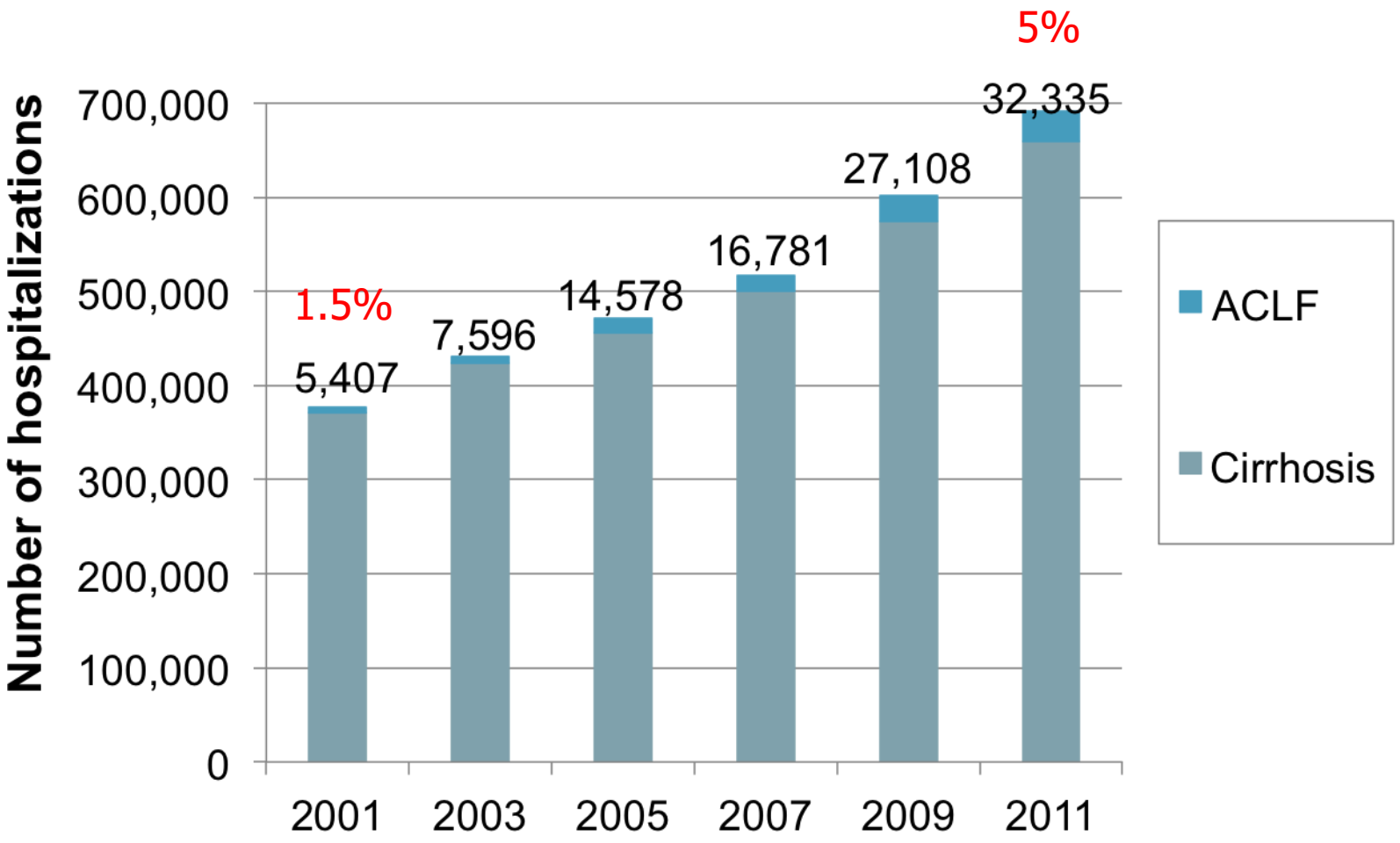
Plan

- What is decompensated Cirrhosis
- Stratification
  - Traditional acute decompensation vs Acute on chronic Liver failure
- Are all decompensating events the same?
    - Infection
    - Variceal Bleeding
    - Ascites
    - Hepatic encephalopathy
- Pathobiology: AD vs ACLF
  - Systemic Inflammation
  - Organs
- Endpoints-
  - Mortality, Cause-specific mortality, Surrogates
  - Hospitalization rates and readmission
  - QOL

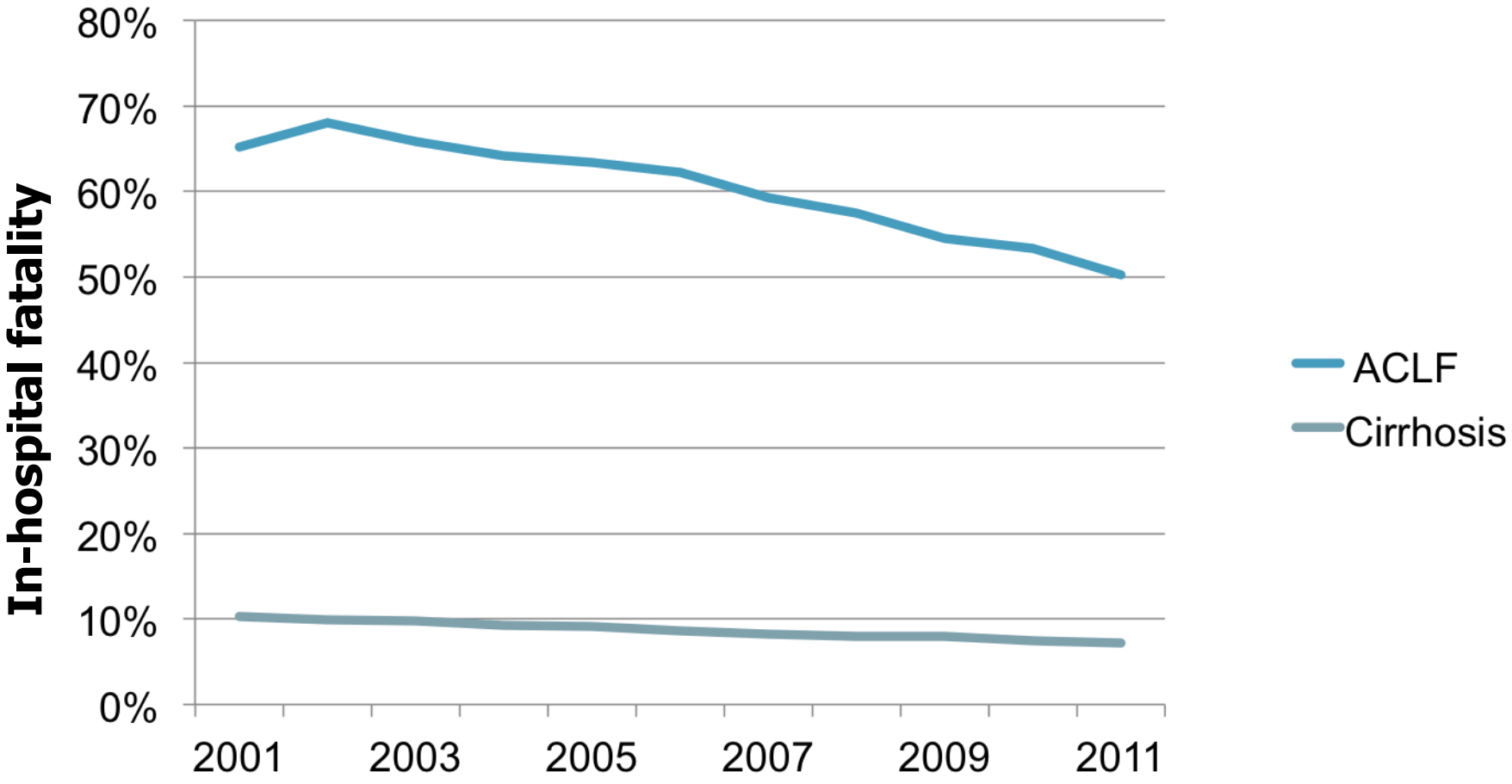
The Cirrhosis Landscape



Increasing Number of Hospitalizations for ACLF and Cirrhosis



Mortality Trends



Economic Burden of ACLF

	Total cost per year	Mean cost per hospitalization	Hospitalizations /year	LOS	Mortality
Cirrhosis	10 bill	14,894	658,884	7	7%
ACLF	1.8 bill	51,841	32,335	16	50%
Pneumonia	$17 billion (all costs)	4,913	1.1 million	5.2	4.1%
CHF	$32 bill? (all costs)	10,775	1 million	5	5.3%
Sepsis	$24.3 billion	19,330	808,000	8.8	

CDC 2010
http://www.cdc.gov/nchs/fastats/pneumonia.htm.

What is ACLF?

AASLD/EASL Working Definition

– ***"acute deterioration of preexisting chronic liver disease usually related to a precipitating event and associated with increased mortality at three months due to multisystem organ failure."***

The CLIF Organ Failure score for diagnosis of ACLF

Organ System	Score = 1	Score = 2	Score = 3
Liver (mg/dl)	Bilirubin < 6	6 ≤ Bilirubin ≤ 12	Bilirubin >12
Kidney (mg/dl)	Creatinine <2	Creatinine ≥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 ≤ 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	≤300 - > 200 >214- ≤357	≤200 ≤214

Values at Study Enrolment. Highlighted area reflects the definition of each organ failure.

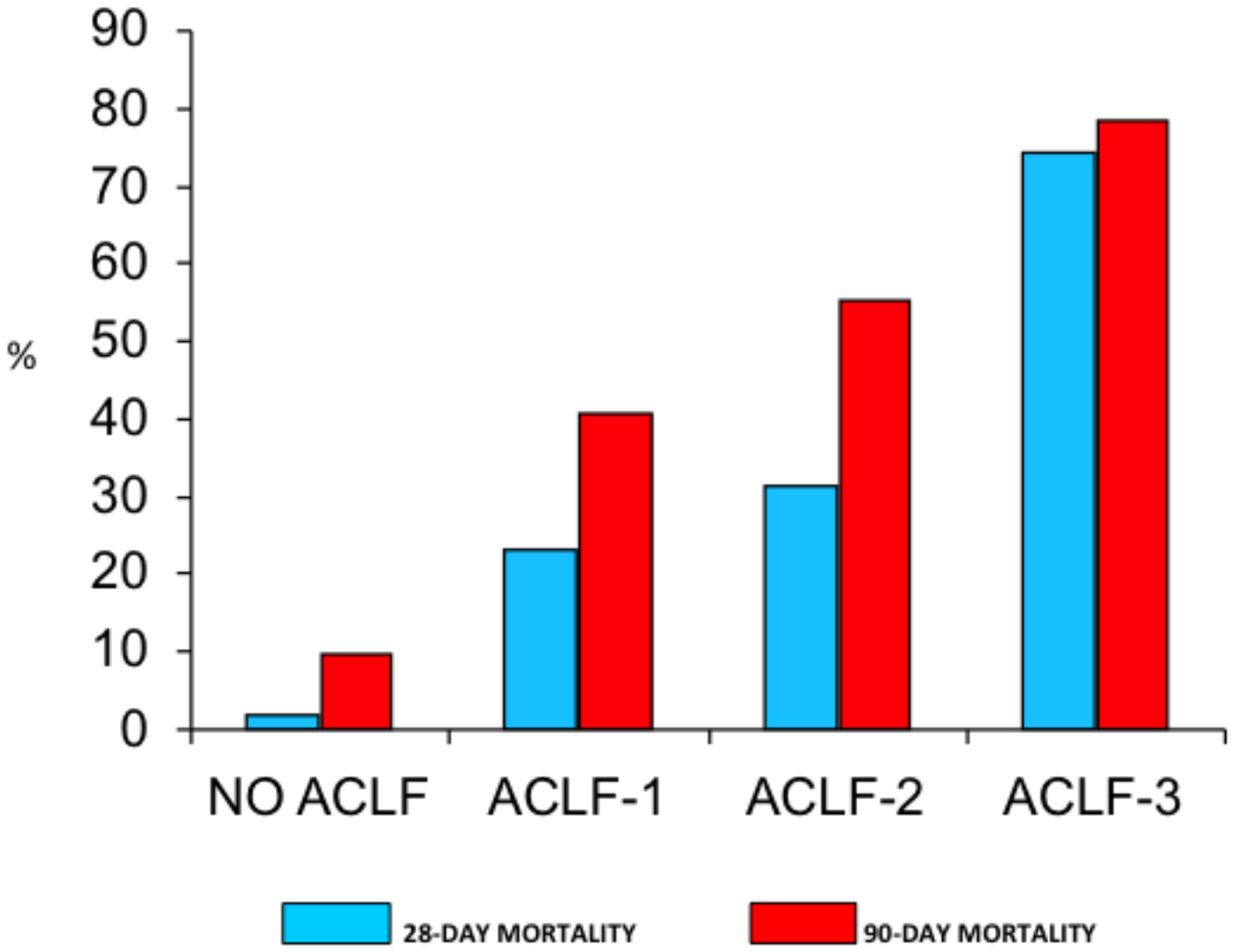
Jalan, Pavesi, Gines et al. JHEP 2014

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 mg/dl and no HE
  - Patient with cerebral failure and serum creatinine <1.5 mg/dl
- **ACLF 1**
  - Patients with renal failure
  - Patients with other single organ failure with
    - serum creatinine ≥1.5 and<2 mg/dl and/or
    - HE grade 1-2.
- **ACLF 2**
  - Patients with 2 organ failures
- **ACLF 3**
  - Patients with 3 or more organ failures

Moreau, Jalan, Pavesi et al. Gastroenterology 2013

28-day and 90-day mortality in ACLF



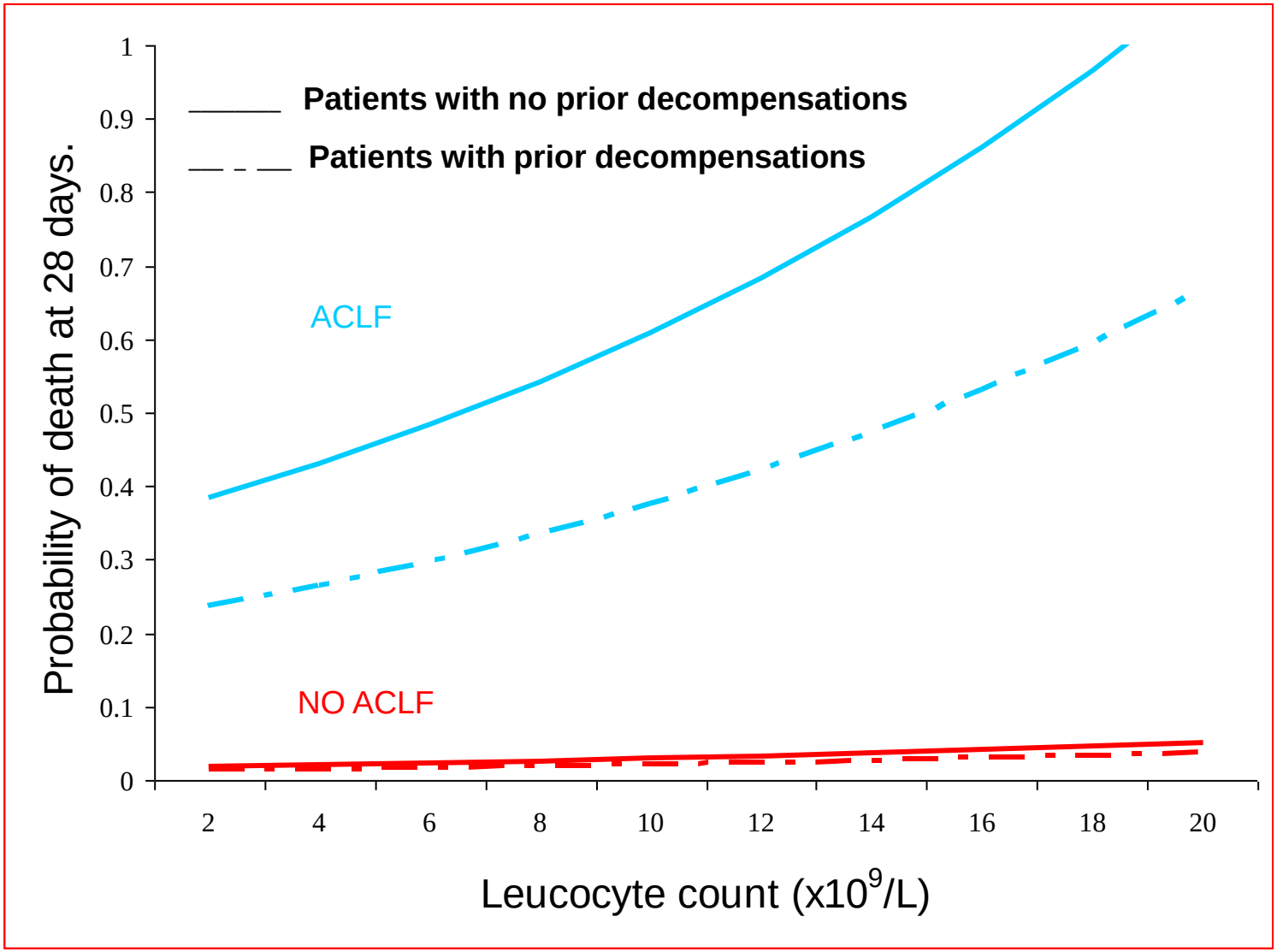
Moreau, Jalan, Pavesi et al. Gastroenterology 2013

Reversing ACLF is likely to improve survival

INITIAL GRADE	FINAL GRADE			
	No ACLF (n=165)	ACLF-1 (n=70)	ACLF-2 (n=59)	ACLF-3 (n=94)
ACLF -1				
Prevalence (n=202)	110 (54.5%)	49 (24.3%)	18 (8.9%)	25 (12.4%)
28-day tx-free mortality (n=190)	7/104 (6.7%)	10/47 (21.3%)	8/15 (53.3%)	21/24 (87.5%)
ACLF -2				
Prevalence (n=136)	47 (34.6%)	19 (14.0%)	35 (25.7%)	35 (25.7%)
28-day tx-free mortality (n=118)	1/42(2.4%)	2/17(11.8%)	8/27 (29.6%)	29/32 (90.63%)
ACLF -3				
Prevalence (n=50)	8 (16.0%)	2 (4.0%)	6 (12%)	34 (68%)
28-day tx-free mortality (n=45)	1/8 (12.5%)	0/2 (0.0%)	4/6 (66.7%)	28/29 (96.6%)

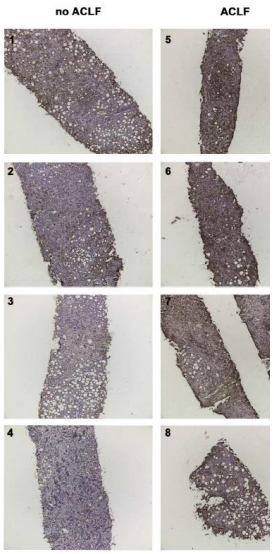
What is different about ACLF?

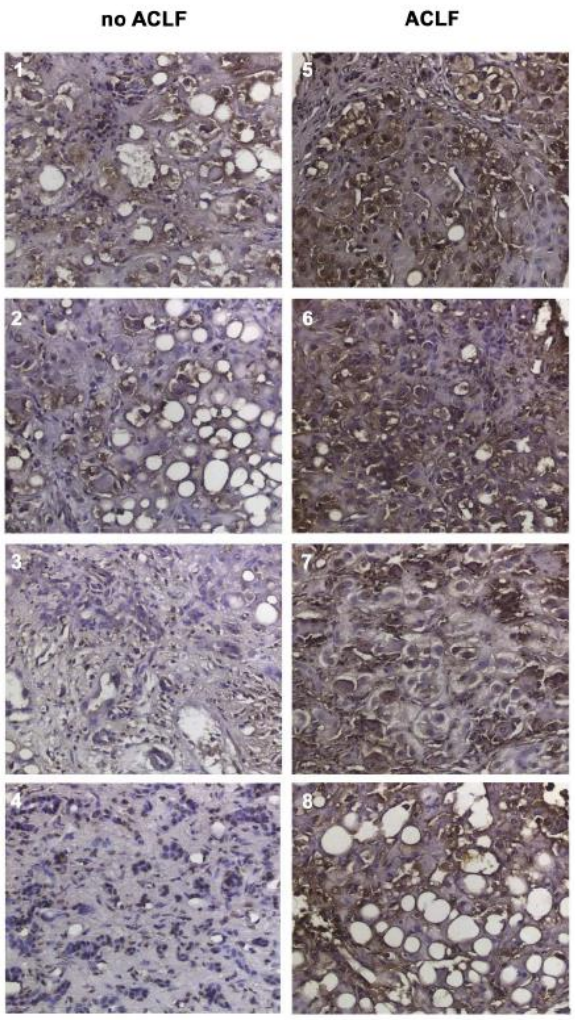
Systemic Inflammation and altered host response is the key difference



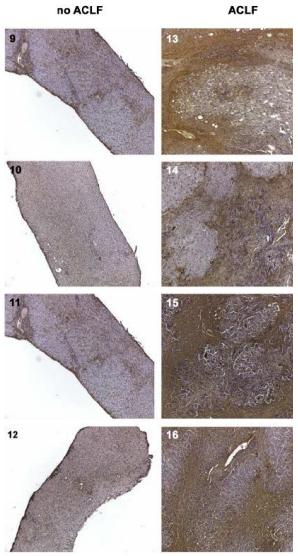
Evidence of increased cell death in ACLF

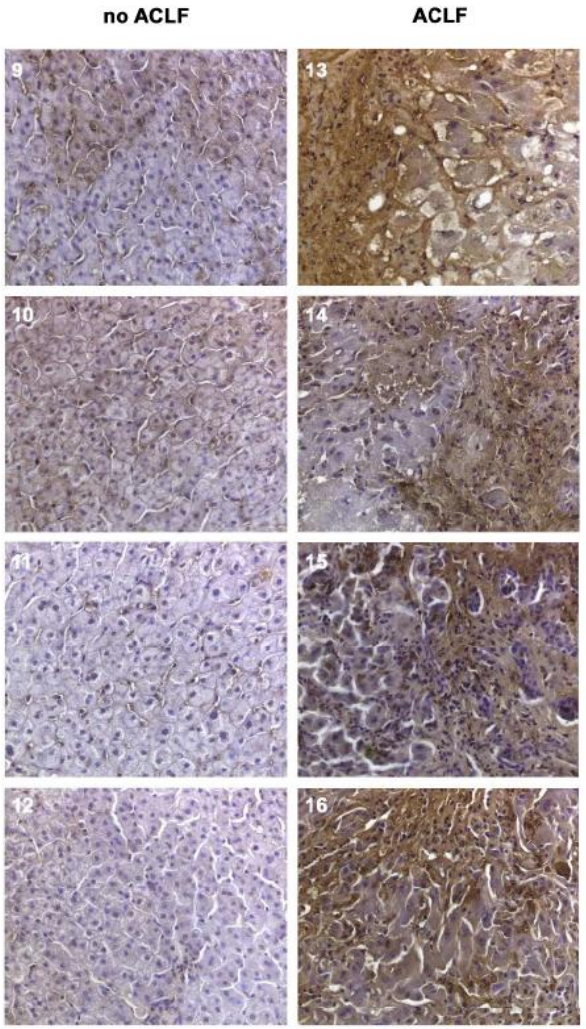
Alcohol





Hepatitis B





Macdonald et al. Hepatology 2017 (in press)

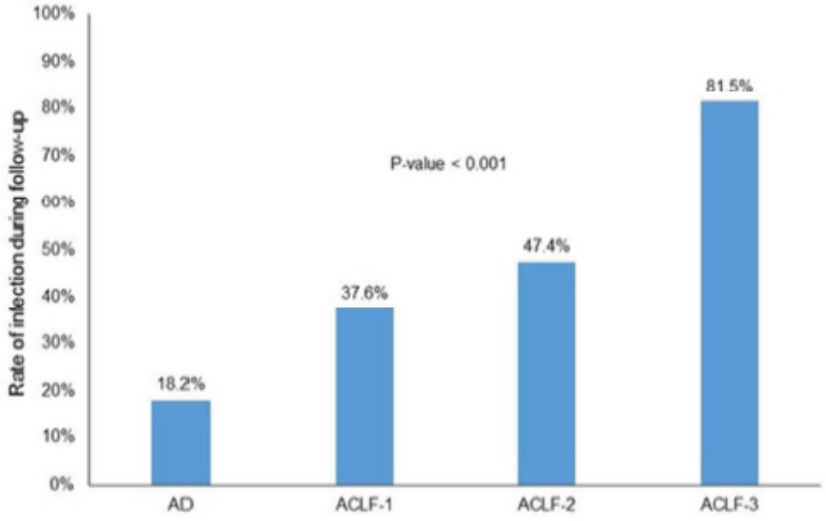
Clinical and biological features of acute decompensating event and the role of ACLF

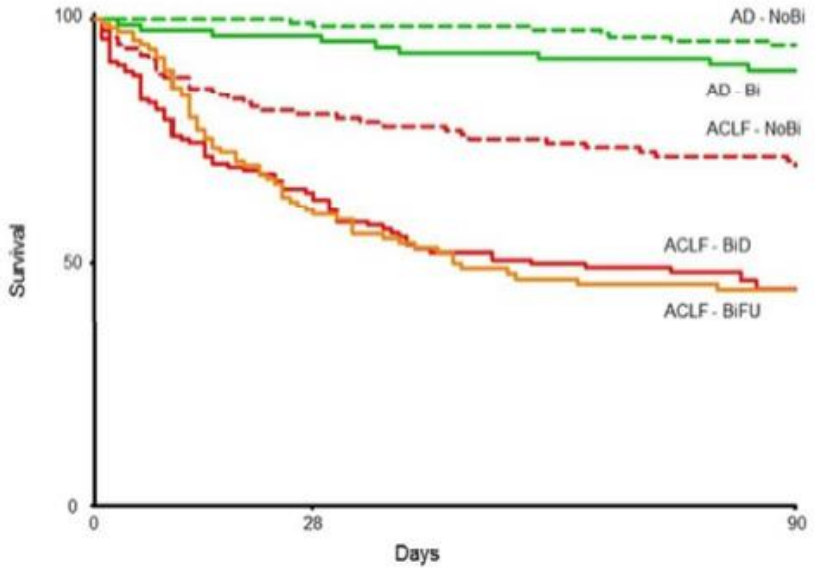
Bacterial infection and active alcoholism are common precipitating illnesses

	NO ACLF (n=862)	ACLF-1 (n=213)	ACLF-2 (n=146)	ACLF 3 (n=56)
Bacterial Infection ‡	185 (21.5%)	61 (28.9%)	43 (29.7%)	23 (41.1%)
GI Bleeding	147 (17.1%)	26 (12.2%)	21 (14.4%)	12 (21.4%)
Active alcoholism* ‡	113 (13.8%)	31 (15.8%)	36 (26.7%)	21 (37.5%)
Other PE †**	27 (3.3%)	16 (8.0%)	12 (8.5%)	3 (5.6%)

* Within 3 months prior to inclusion;
** Other PE: therapeutic paracentesis without albumin, TIPS, major surgery, acute hepatitis and acute alcoholic hepatitis.
*** Bacterial Infections, Active Alcoholism or Other PE's ;
Overall comparison across ACLF categories. †: $p<0.05$; ‡: $p<0.001$

Risk of new infection and attendant mortality is greater in ACLF patients





Fernandez et al. Gut 2017

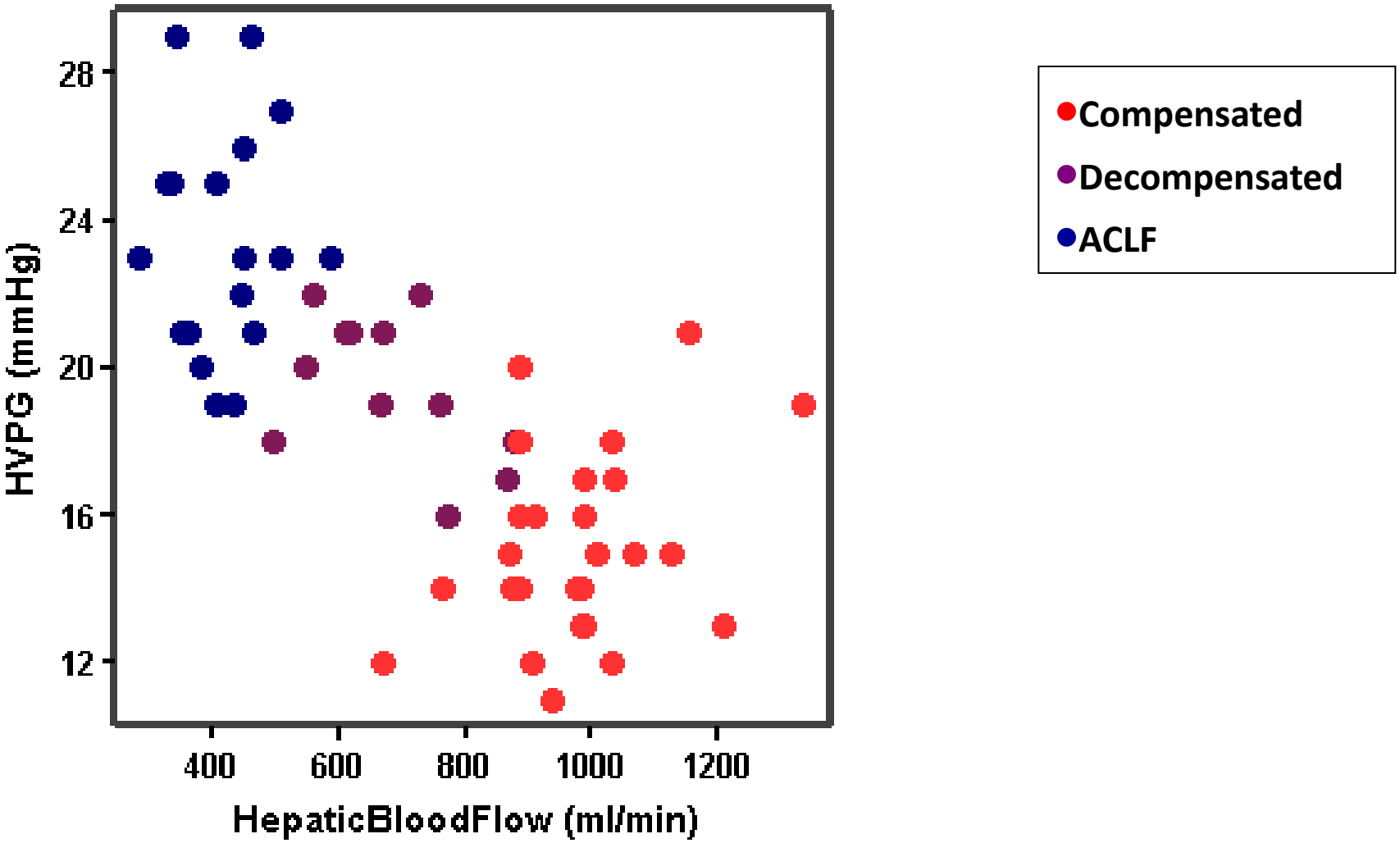
Variceal bleeding mortality is context specific and organ dysfunction exacerbates risk of death

GI BLEEDING, ACLF AND MORTALITY

	28-day mortality	90-day mortality
No ACLF (n=181)	2.8%	7.6%
ACLF (n=41)	46.3%	48.8%

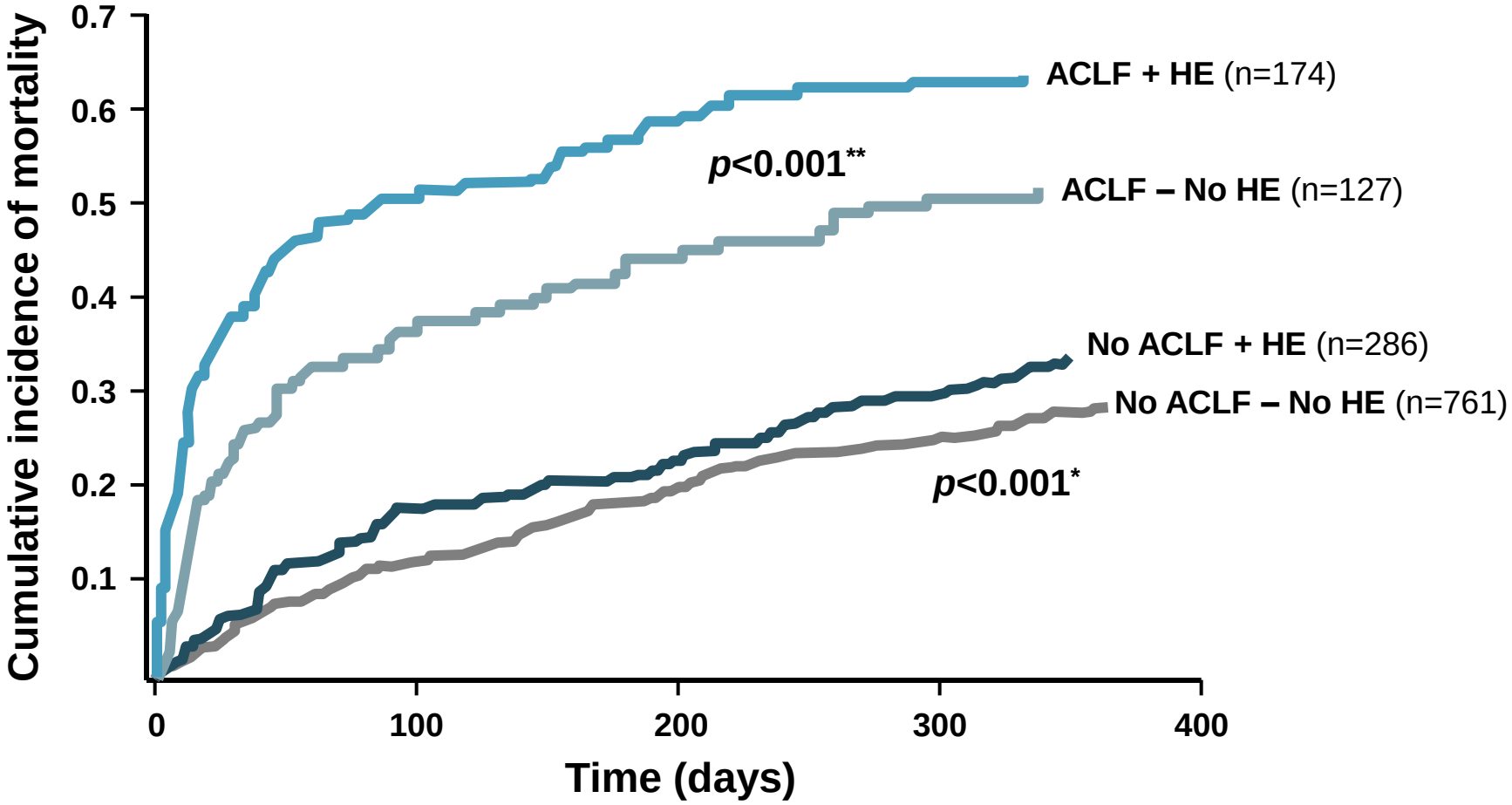
Data from CANONIC study

Is HVPG a surrogate?



Mehta et al. Liver international, 2014

The presence of ACLF alters the natural history of Hepatic Encephalopathy



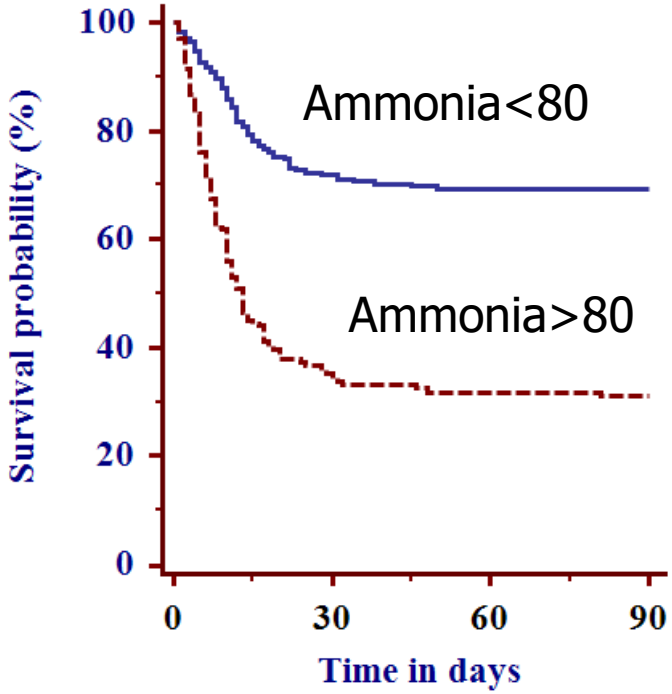
Competing risk assessment

***p-value comparing presence vs absence of HE in patients without ACLF**

****p-value comparing presence vs absence of HE in patients with ACLF**

Adapted from Cordoba J *et al. J Hepatol* 2014;60:275–81

Is ammonia levels a surrogate for HE?



Number at risk

Group: ammonia < 80 µmol/L

282 169 148 94

Group: ammonia ≥ 80 µmol/L

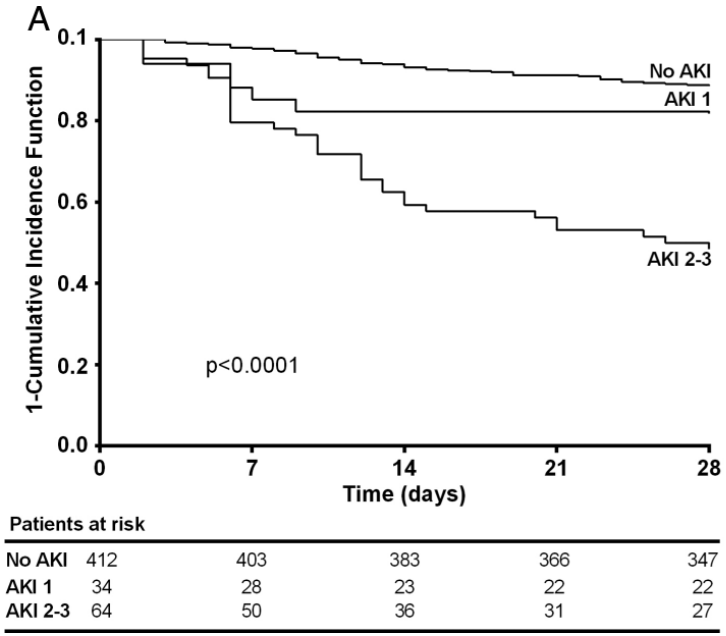
248 63 45 5

			ammonia change		
			Improved	same	Worsened
Survial	Survived	Count	15	4	10
		%	51.7%	13.8%	34.5%
	Dead	Count	13	13	30
		%	23.2%	23.2%	53.6%

❑ In the 57 patients in whom ammonia levels remained unchanged or worsened, 43 died (75%)

AASLD 2017, Poster 503

Outcome of AKI is determined by the severity of ACLF



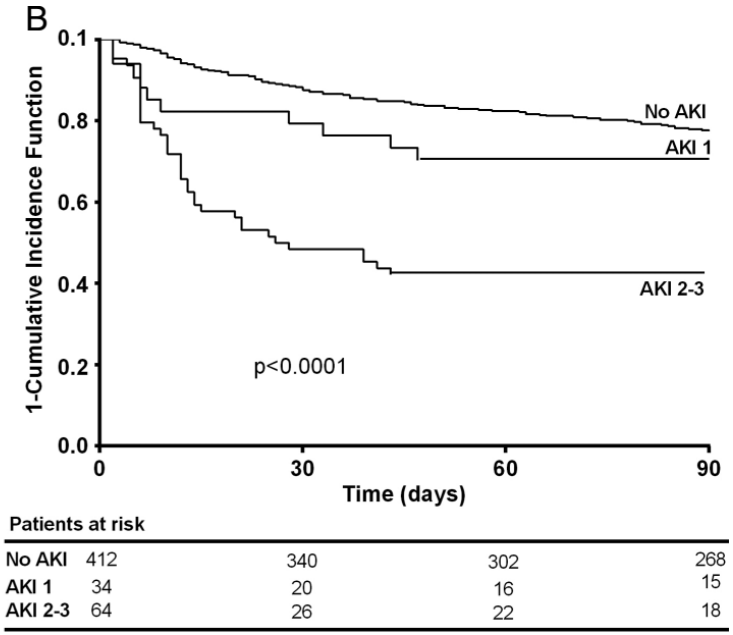


Table 5 Comparison of acute kidney injury (AKI) and acute-on-chronic liver failure (ACLF) classifications to predict 28-day and 90-day mortality

	AKI	ACLF at enrolment	ACLF at 48 h	AKI vs ACLF at enrolment	AKI vs ACLF at 48 h	ACLF at enrolment vs ACLF at 48 h
AUCROC*					p Value	
28-day	0.68 (0.62 to 0.73)	0.77 (0.71 to 0.82)	0.84 (0.80 to 0.89)	0.0049	<0.0001	0.0021
90-day	0.62 (0.57 to 0.66)	0.72 (0.67 to 0.77)	0.77 (0.73 to 0.82)	<0.0001	<0.0001	0.0092
C-index†					p Value	
28-day	0.66 (0.61 to 0.71)	0.74 (0.69 to 0.79)	0.81 (0.76 to 0.85)	0.09	<0.0001	0.0004
90-day	0.61 (0.57 to 0.65)	0.69 (0.65 to 0.73)	0.74 (0.70 to 0.77)	0.0028	<0.0001	0.0002

Values in parentheses are 95% CIs.
*Transplant-free mortality.
†Mortality considering transplantation as competing event.
AUCROC, area under the curve of the receiving operating characteristic.

Angeli et al. Gut 2015

What is the prognosis?

Independent Factors associated with Mortality for the ACLF patients

- CLIF-C OF score
- Age
- Ln White-cell count

CLIF-C ACLF Score [0-100]

10*[0.33*CLIF-OFs + 0.04*Age + 0.63*Ln WCC – 2]

Probability of death at time "t"

$$P = 1 - e^{(-CI(t) * \exp(\beta(t) * \text{CLIF-C ACLFs}))}$$

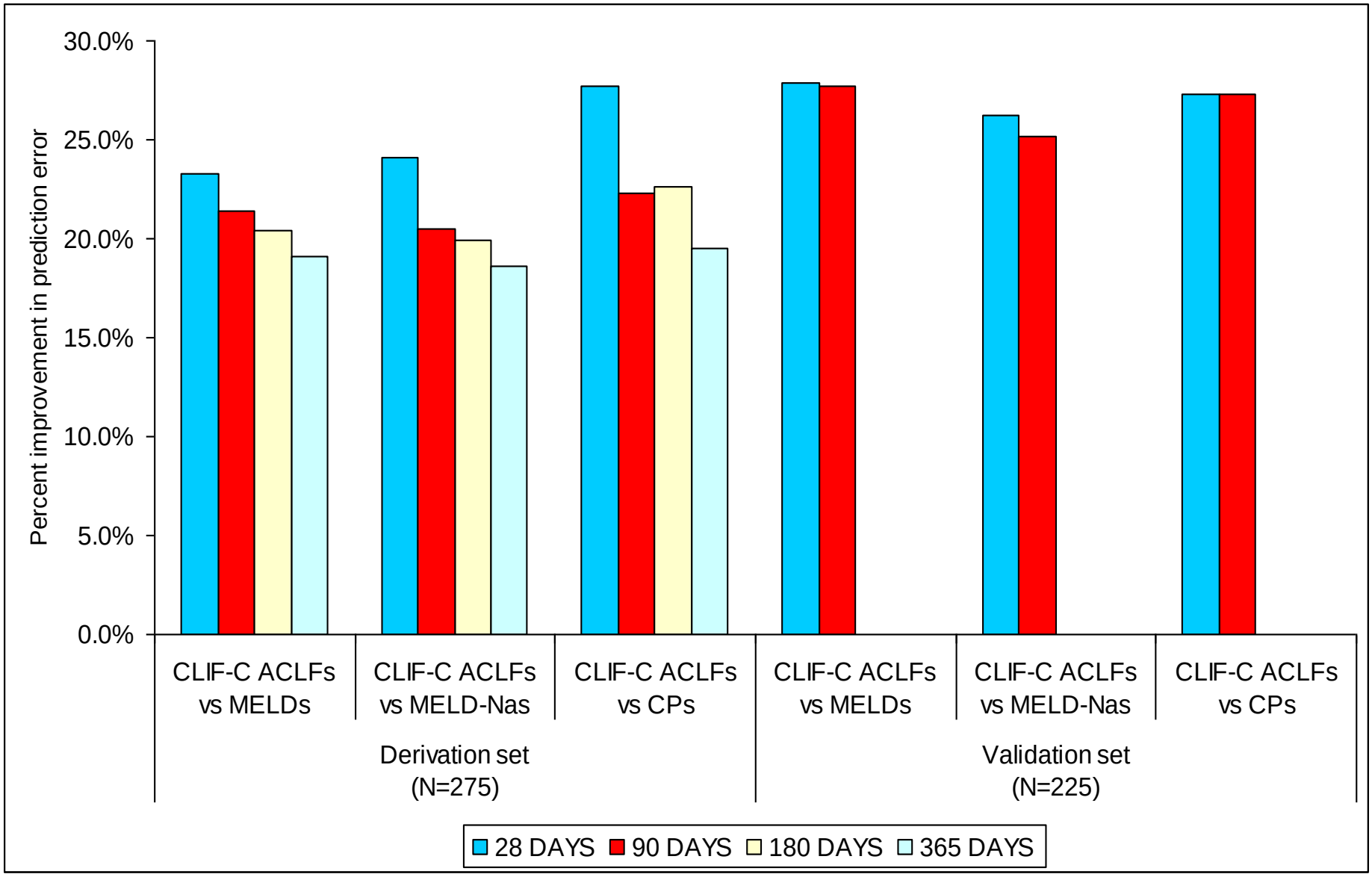
Jalan, Pavesi, Gines et al. JHEP 2014

Performance and Validation of the CLIF-C ACLF score (C-index 95%CI)

	CLIF ACLF	Child-Pugh	MELD	MELD-Na
CANONIC PATIENTS (N=275)				
28-Day mortality	0.760	0.668	0.687	0.684
p-value vs CLIF-C*		<0.001	<0.001	<0.001
90-Day mortality	0.732	0.655	0.659	0.663
p-value vs CLIF-C*		<0.001	<0.001	0.001
VALIDATION DATABASE (n=225)				
28-Day mortality	0.744	0.653	0.645	0.648
p-value vs CLIF-C*		<0.001	<0.001	<0.001
90-Day mortality	0.736	0.647	0.635	0.637
p-value vs CLIF-C*		<0.001	<0.001	<0.001

Jalan, Pavesi, Gines et al. JHEP 2014

CLIF-C ACLF score improves the performance of the MELD, MELD Na and CP scores



Jalan, Pavesi, Gines et al. JHEP 2014

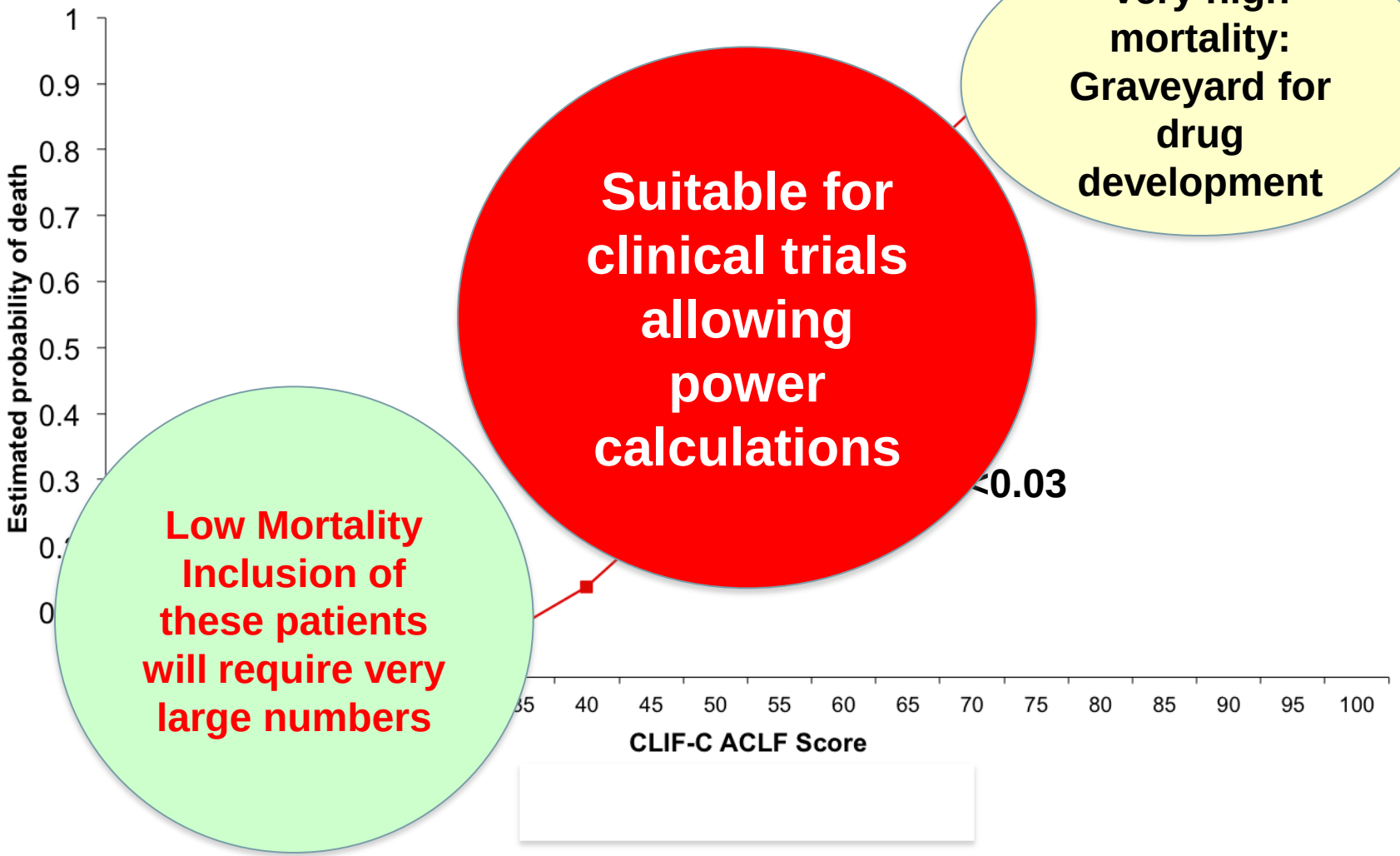
Can a change in the CLIF-ACLF and MELD scores be used as surrogates?

28-Day mortality:	Survivors	Dead	p-value
Mean change in MELD	-0.82 (5.58)	+3.06 (6.28)	<0.001
Mean change in CLIF-C ACLFs	-3.04 (6.96)	+5.13 (9.6)	<0.001

90-Day mortality:	Survivors	Dead	p-value
Mean change in MELD	-0.95 (5.66)	+2.01 (6.14)	<0.001
Mean change in CLIF-C ACLFs	-3.23 (7.52)	+2.61 (8.77)	<0.001

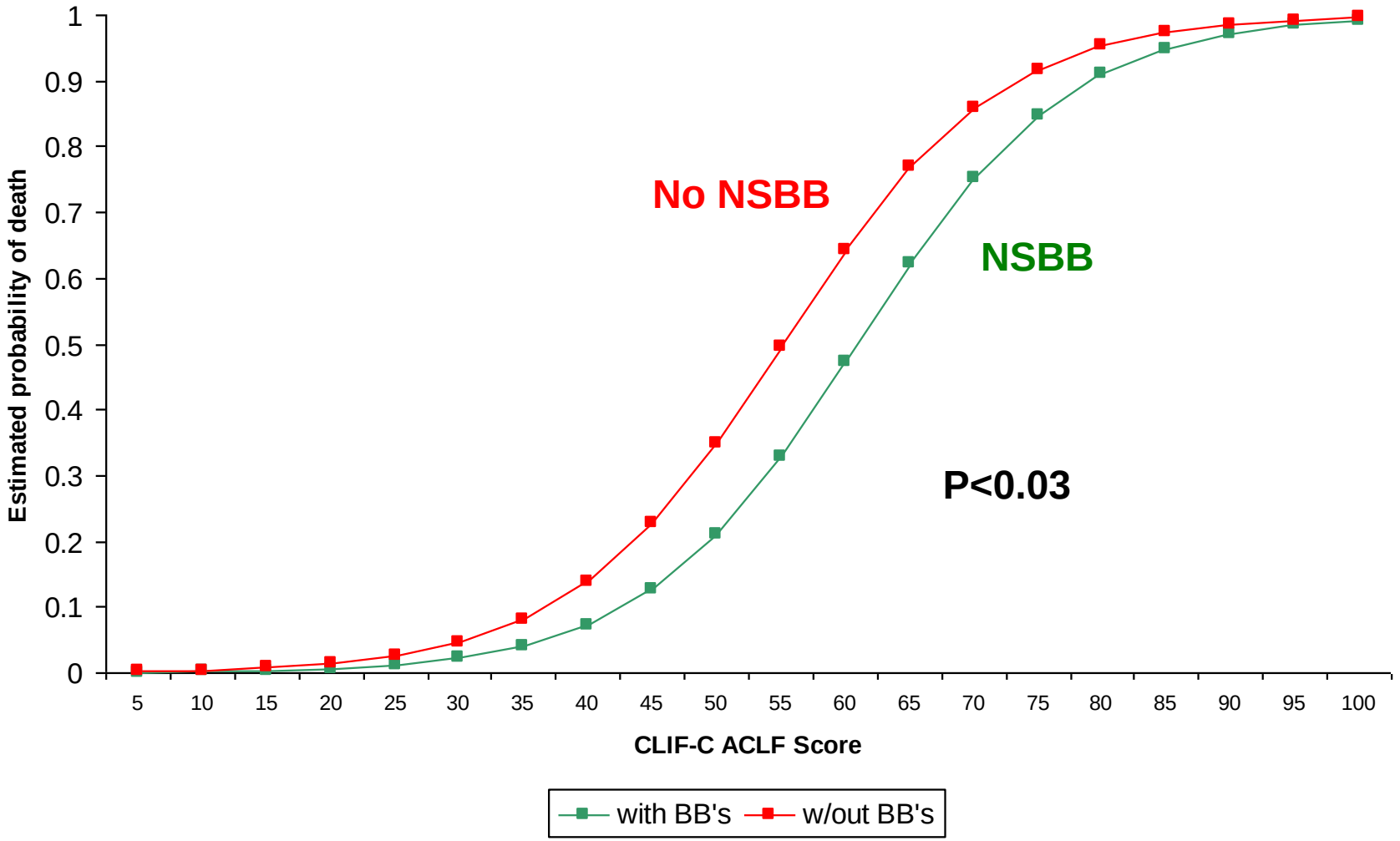
□

Patient selection in clinical trials



Mookerjee et al. JHEP 2015

How can the CLIF-ACLF score be used in drug development….



Mookerjee et al. 2015 (JHEP 2016)

Independent Factors associated with Mortality for the AD patients

- Age
- Serum sodium
- Ln White-cell count
- Ln Creatinine
- Ln INR

CLIF-C AD Score [0-100]

10*0.03*Age +
0.66*Ln Creatinine +
1.71*Ln INR +
0.88*Ln WBC +
-0.05*Sodium + 8

Probability of death at time "t"

$$P = 1 - e^{(-CI(t) * \exp(\beta(t) * \text{CLIF-C ADs}))}$$

Performance of the CLIF-C AD score (C-index 95%CI)

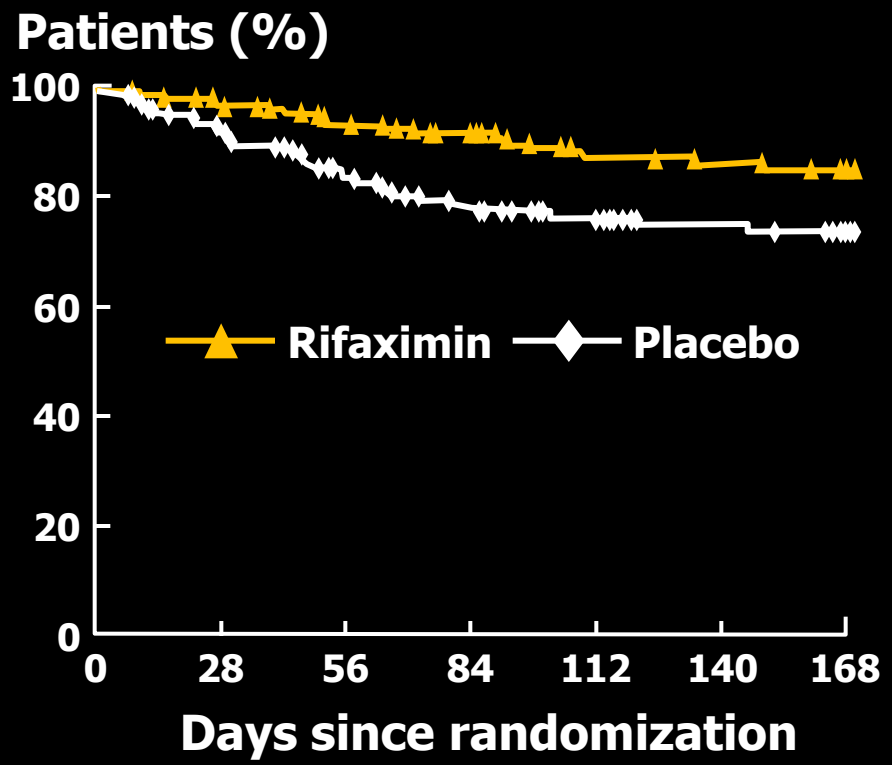
	CLIF-AD	MELD	MELD-Na	Child-Pugh
CANONIC PATIENTS (N=1016)				
28-Day mortality	0.764 (0.688-0.825)	0.700(0.629-0.771)	0.725(0.651-0.800)	0.698(0.617-0.779)
p-value vs CLIF-C*		0.004	0.064	0.071
90-Day mortality	0.743(0.704-0.783)	0.649(0.602-0.697)	0.681(0.633-0.728)	0.651(0.601-0.701)
p-value vs CLIF-C*		<0.001	<0.001	<0.001
VALIDATION DATASET (n=328)				
90-Day mortality	0.782 (0.725-0.839)	0.595 (0.487-0.702)	0.653 (0.550-0.755)	0.649 (0.566-0.732)
p-value vs CLIF-C*		0.0007	0.0136	0.0018

Other Outcomes

- **Resource ultilisation**
  - ***Hospitalization rates***
    - Requirement for ICU admission (?)
    - Recovery from severity of HE (MARS)
  - ***Hospital Readmissions***
    - Clear regulatory path: Rifaximin
- **QOL as an end point in decompensated cirrhosis patients**

Rifaximin for Secondary Prophylaxis of HE: Hospitalization

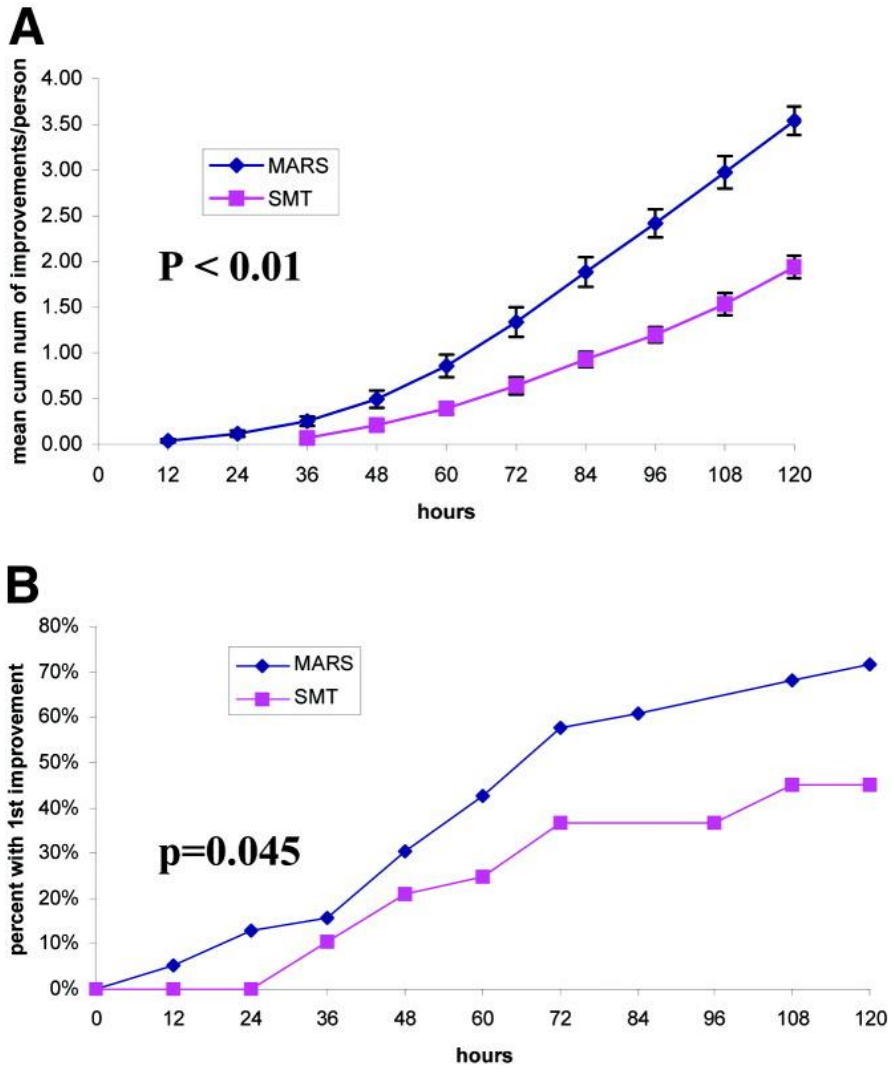
Time to first HE-related hospitalization (Key secondary endpoint)



Hazard ratio with rifaximin, 0.50
(95% CI, 0.29–0.87)
p=0.01

Bass et al, N Engl J Med, 2010;362:1071–81.

Time to improvement of HE with MARS led to it receiving regulatory approval



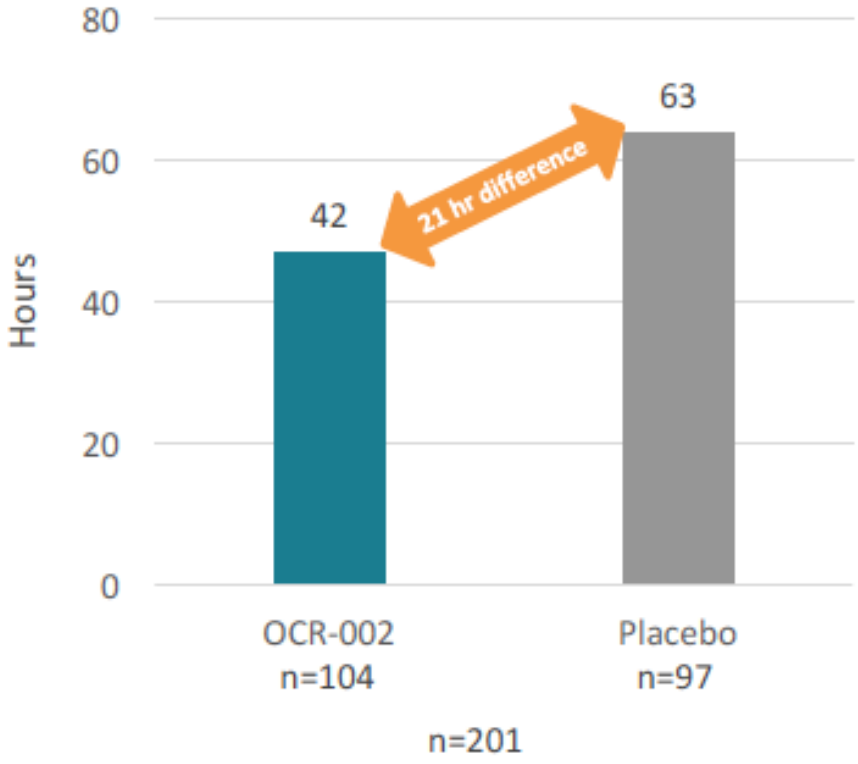
Survival

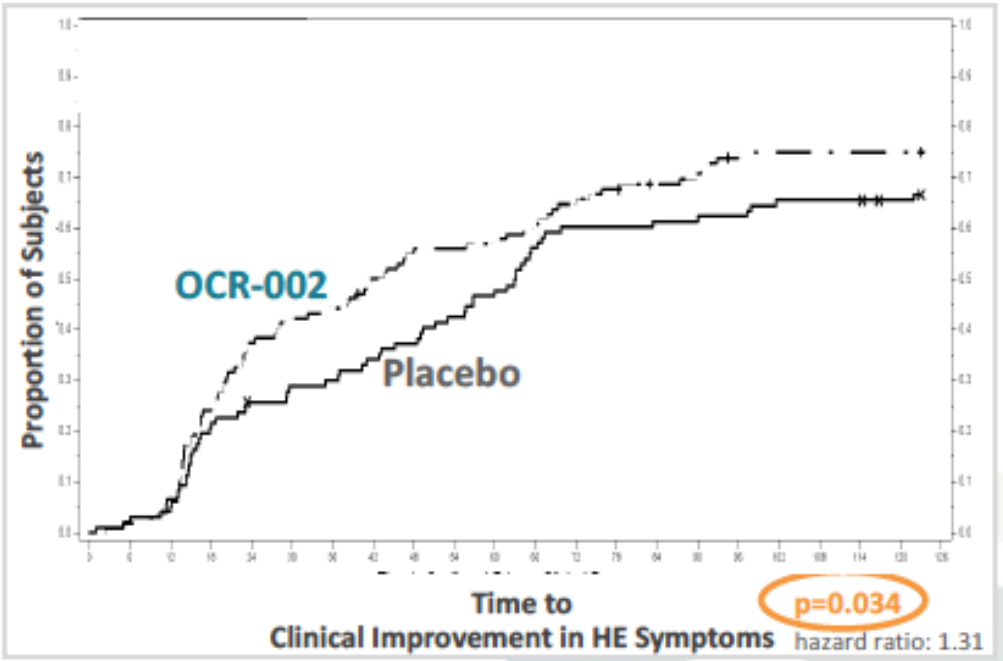
2 and 4 week survival were significantly greater in the responders compared with non-responders

Hassanein et al. Hepatology 2007

STOP-HE Primary Endpoint: Post Hoc Analysis

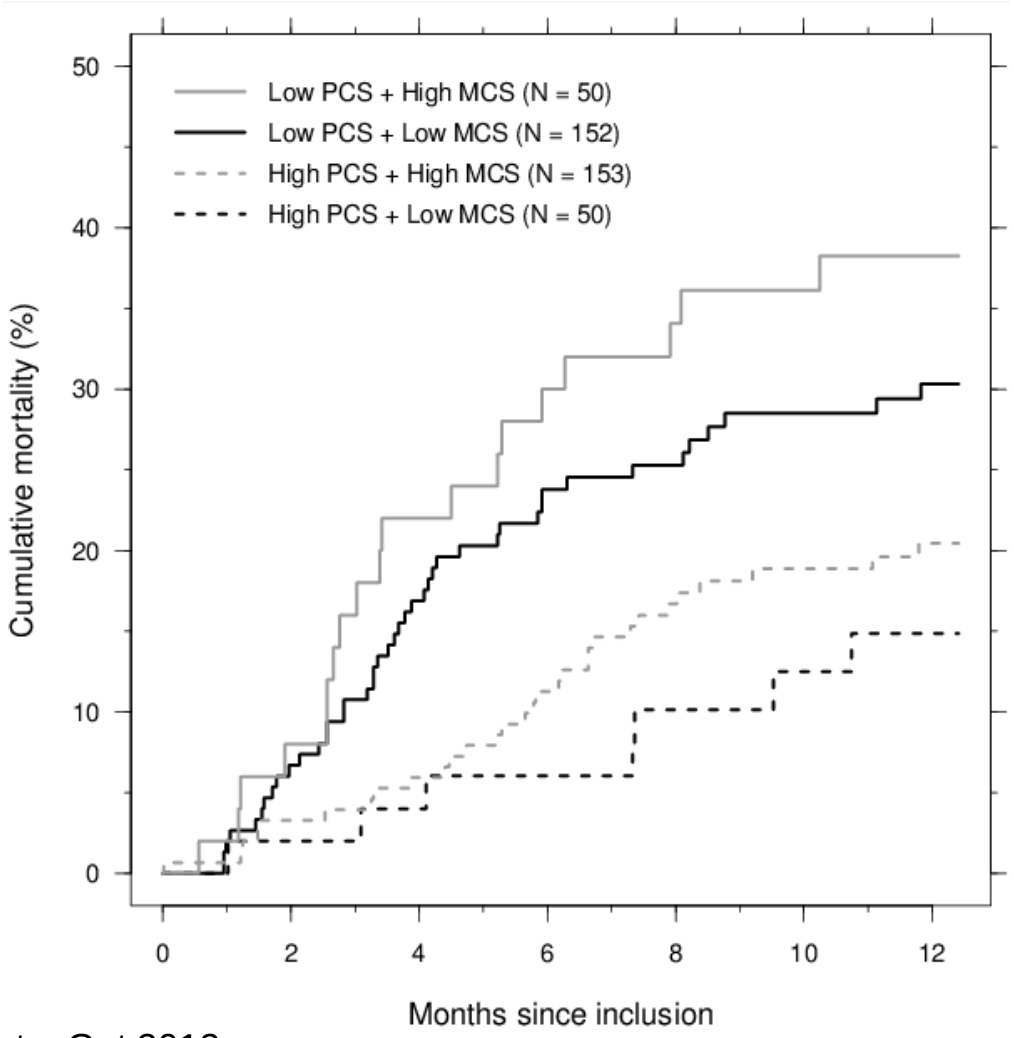
Median Time to Clinical Improvement in HE Symptoms in Patients with Confirmed Baseline Ammonia >ULN





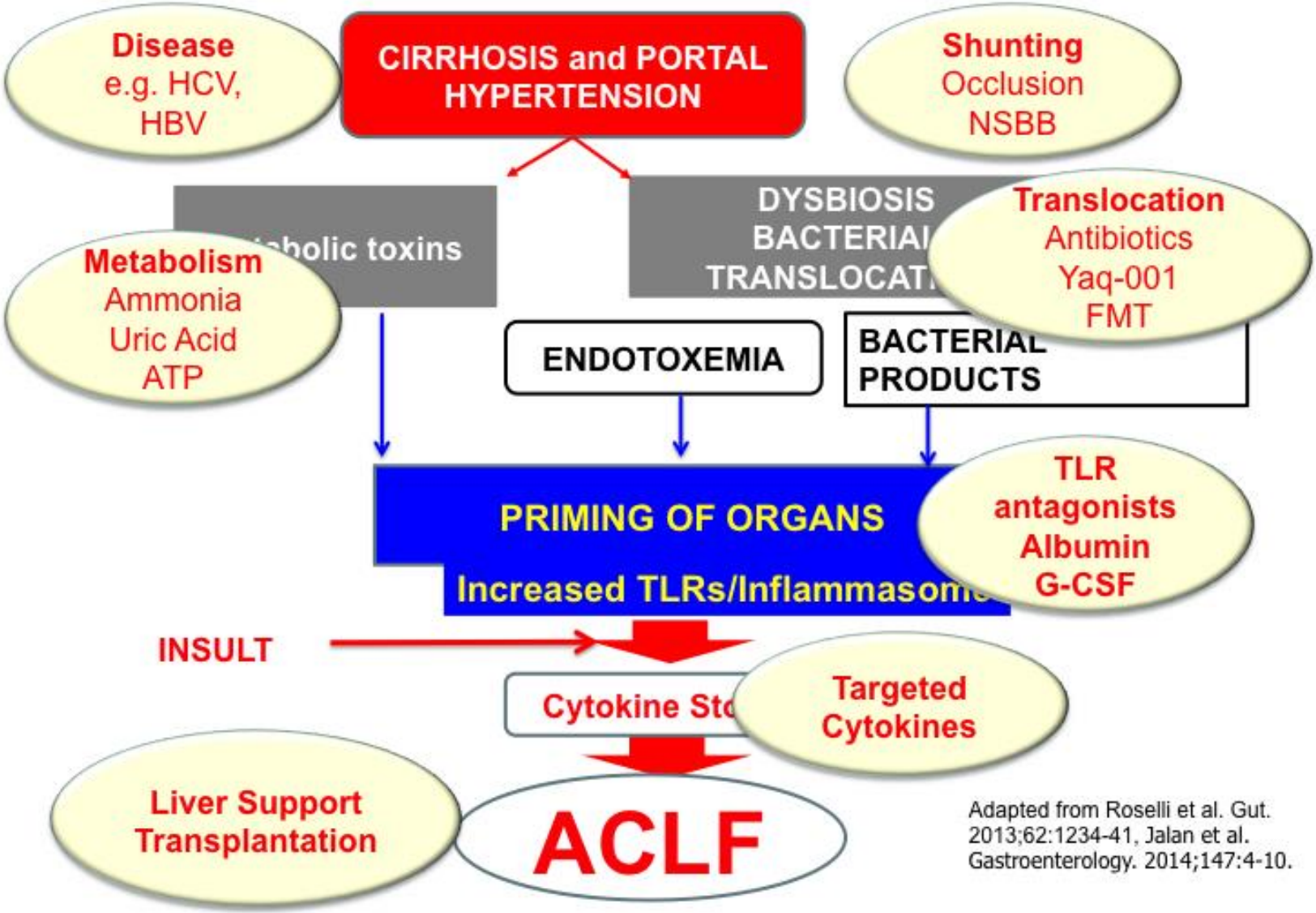
Per Protocol Population Showed High Statistical Significance; p=0.034

Quality of life measures as a surrogate for survival in patients with refractory ascites



re-analysis of satavaptan data, Gut 2012

In Europe 9 Clinical Trials are focusing on AD and ACLF patients at high risk of death



Adapted from Roselli et al. Gut. 2013;62:1234-41, Jalan et al. Gastroenterology. 2014;147:4-10.

Summary

- In patients with acute decompensation of cirrhosis, ACLF defines the natural history and the underlying pathophysiology
- In patients with traditional AD and ACLF, the CLIF-C scores are currently the best available clinical prognostic markers
- A change in MELDs and the CLIF-ACLFs at day 5-7 are surrogates for mortality in ACLF patients
- Urgent need for biomarkers
  - HVPG: Not appropriate
  - Ammonia: Potential but needs more data
- Other outcomes that are relevant are
  - Reducing hospitalisation / ICU duration
  - Hospital readmission is a clear end point: Rifaximin
  - QoL: especially in patients with refractory ascites