ACUTE ON CHRONIC LIVER FAILURE: FROM A TO CLF

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Evolving Cirrhosis
setting the stage to ACLF
DECOMPENSATION OF CIRRHOSIS
a decisive time point both in terms of medical management and prognosis

Chronic liver disease → Compensated cirrhosis → Decompensated cirrhosis → Death

Development of complications

- Ascites
- Variceal bleeding
- Encephalopathy
- Jaundice
- Bacterial infections
IMPACT OF DECOMPENSATION ON PROGNOSIS

Gines et al. Hepatology 1987; 7:122
ACLF : A SEPARATE ENTITY

... which does not equal end-stage liver disease !!!
Acute-on-chronic Liver Failure • High mortality (1 month) • Multiple organ or systems failure • Immune dysfunction

Organ/system FAILURE
- Liver
- Coagulation
- Kidney
- Brain
- Circulation
- Lung

ACLF: A SEPARATE ENTITY
... and which not equals end-stage liver disease!!!
Definition, Diagnosis and Grading
ACLF : The EASL-CLIF Consortium definition

acute decompensation of cirrhosis
(defined by the development of ascites, HE, GI bleeding and/or bacterial infections)

+ 

single organ failure
  • single renal failure or
  • other single non-renal organ failure if associated with renal and/or brain dysfunction

multiple organ failures.

Moreau R et al Gastroenterology 2013
Acute-on-Chronic Liver Failure Is a Distinct Syndrome That Develops in Patients With Acute Decompensation of Cirrhosis

RICHARD MOREAU, RAJIV JALAN, PERE GINES, MARCO PAVESI, PAOLO ANGELI, JUAN CORDOBA, FRANCOIS DURAND, THIERRY GUSTOT, FAOUZI SALIBA, MARCO DOMENICALI, ALEXANDER GERBES, JULIA WENDON, CARLO ALESSANDRIA, WIM LALEMAN, STEFAN ZEUZEM, JONEL TREBICKA, MAURO BERNARDI, and VICENTE ARROYO, for the CANONIC Study Investigators of the EASL–CLIF Consortium

GASTROENTEROLOGY 2013;144:1426–1437

Figure 1. Screening, enrollment, and flow of patients according to the presence or absence of ACLF.
**DIAGNOSIS & GRADING OF ACLF**

The *diagnosis* and the *grading* of ACLF is based on the SOFA score.

<table>
<thead>
<tr>
<th>Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>System</strong></td>
</tr>
<tr>
<td>Respiration</td>
</tr>
<tr>
<td>Coagulation</td>
</tr>
<tr>
<td>Liver</td>
</tr>
<tr>
<td>Cardiovascular</td>
</tr>
<tr>
<td>Central nervous system</td>
</tr>
<tr>
<td>Renal</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: $\text{FiO}_2$, fraction of inspired oxygen; MAP, mean arterial pressure; $\text{Pao}_2$, partial pressure of oxygen.

b Catecholamine doses are given as μg/kg/min for at least 1 hour.

c Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

*a Adapted from Vincent et al. 27*
DIAGNOSIS & GRADING OF ACLF

...but slightly adapted to the liver setting!
**DIAGNOSIS & GRADING OF ACLF**

and finally simplified to the CLIF-C SOFA score which defines ($\geq 7$ – max 18) and grades ACLF

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Score = 1</th>
<th>Score = 2</th>
<th>Score = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver, bilirubin (mg/dl)</td>
<td>$&lt;6$</td>
<td>$6-\leq 12$</td>
<td>$&gt;12$</td>
</tr>
<tr>
<td>Kidney, creatinine (mg/dl)</td>
<td>$&lt;2$</td>
<td>$2-&lt;3.5$</td>
<td>$\geq 3.5$ or renal replacement</td>
</tr>
<tr>
<td>Brain, grade (West-Haven)</td>
<td>0</td>
<td>1-2</td>
<td>3-4</td>
</tr>
<tr>
<td>Coagulation, INR</td>
<td>$&lt;2.0$</td>
<td>2.0-&lt;2.5</td>
<td>$\geq 2.5$</td>
</tr>
<tr>
<td>Circulation, MAP (mmHg)</td>
<td>$\geq 70$</td>
<td>$&lt;70$</td>
<td>Vasopressors</td>
</tr>
<tr>
<td>Respiratory $\text{PaO}_2/\text{FiO}_2$</td>
<td>$&gt;300$</td>
<td>$\leq 300$ and $&gt;200$</td>
<td>$\leq 200$</td>
</tr>
<tr>
<td>or $\text{SpO}_2/\text{FiO}_2$</td>
<td>$&gt;357$</td>
<td>$&gt;214$ and $\leq 357$</td>
<td>$\leq 214$</td>
</tr>
</tbody>
</table>

Jalan et al. J Hepatol 2014 and 2015
## GRADES OF ACLF

<table>
<thead>
<tr>
<th>Grade Description</th>
<th>TX-free patients (n = 1,287)</th>
<th>28-d mortality rate</th>
<th>ACLF grades</th>
</tr>
</thead>
<tbody>
<tr>
<td>No organ failure</td>
<td>879 (68.3%)</td>
<td>39/879 (4.4%)</td>
<td>→ No ACLF</td>
</tr>
<tr>
<td>Single nonrenal failure, creatinine &lt; 1.5 mg/dL, no HE</td>
<td>128 (9.9%)</td>
<td>8/128 (6.3%)</td>
<td>→ ACLF-1</td>
</tr>
<tr>
<td>Single renal failure</td>
<td>86 (6.7%)</td>
<td>16/86 (18.6%)</td>
<td></td>
</tr>
<tr>
<td>Single nonrenal failure, creatinine 1.5–1.9 mg/dL and/or HE</td>
<td>54 (4.1%)</td>
<td>15/54 (27.7%)</td>
<td></td>
</tr>
<tr>
<td>2 organ failures</td>
<td>97 (7.5%)</td>
<td>31/97 (32.0%)</td>
<td>→ ACLF-2</td>
</tr>
<tr>
<td>3 organ failures</td>
<td>25 (1.9%)</td>
<td>17/25 (68.0%)</td>
<td>→ ACLF-3</td>
</tr>
<tr>
<td>4–6 organ failures</td>
<td>18 (1.4%)</td>
<td>12/18 (88.9%)</td>
<td></td>
</tr>
</tbody>
</table>

Decompensation of chronic liver disease: a decisive time point with organ dysfunction/failure as enhancer

Moreau R et al. CANONIC-trial. Gastroenterology 2013

Acute decompensation without organ failure (67.1%)
Decompensation of chronic liver disease:
a decisive time point with organ failure as enhancer

Moreau R et al. CANONIC-trial. Gastroenterology 2013
Supplementary Table 7. Main Causes of Death at 28 and 90 Days After Study Enrollment

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>Deaths at 28 days (n = 144)</th>
<th>Deaths at 90 days (n = 265)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple organ failure without septic or hypovolemic shock</td>
<td>63 (43.8)</td>
<td>99 (37.4)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>40 (27.8)</td>
<td>62 (23.4)</td>
</tr>
<tr>
<td>Hypovolemic shock</td>
<td>12 (8.3)</td>
<td>19 (7.2)</td>
</tr>
<tr>
<td>Cirrhosis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>7 (2.6)</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>2 (1.4)</td>
<td>4 (1.5)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (0.7)</td>
<td>4 (1.5)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>1 (0.7)</td>
<td>4 (1.5)</td>
</tr>
<tr>
<td>Non-liver cancer</td>
<td>2 (1.4)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Massive pulmonary inhalation</td>
<td>1 (0.7)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Epileptic status</td>
<td>1 (0.7)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Other causes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7 (4.9)</td>
<td>11 (4.2)</td>
</tr>
<tr>
<td>Cause unknown</td>
<td>11 (7.6)</td>
<td>42 (15.8)</td>
</tr>
</tbody>
</table>
Scores: via www or app
Pathogenesis: a historical perspective
Decompensation: a “hemodynamic” event

The peripheral arterial vasodilation theory

HRS – refract ascites -

Gines P, Shrier RW. NEJM 2009
Decompensation: a “hemodynamic” event

The peripheral arterial vasodilation theory

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<table>
<thead>
<tr>
<th>Compensated Cirrhosis</th>
<th>Decompensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased intrahepatic vascular resistance</td>
<td>Disease progression</td>
</tr>
<tr>
<td>Moderate portal hypertension</td>
<td>Severe portal hypertension</td>
</tr>
<tr>
<td>Splanchnic arterial vasodilation</td>
<td>Bacterial translocation</td>
</tr>
<tr>
<td>Low effective arterial blood volume</td>
<td>Severe splanchnic arterial vasodilatation</td>
</tr>
<tr>
<td>Markedly reduced effective arterial blood volume</td>
<td>Splanchnic arterial vasodilatation</td>
</tr>
<tr>
<td>Increased cardiac output</td>
<td>Sodium and water retention and ascites formation</td>
</tr>
<tr>
<td>Increased plasma volume</td>
<td>Further activation of vasoconstrictor systems</td>
</tr>
<tr>
<td>Restoration of effective arterial blood volume</td>
<td>Impairment in cardiac output</td>
</tr>
</tbody>
</table>

Splanchnic vasodilatation

Effective hypovolemia

Core factor

Primary pathogenetic mechanism

HRS – refract ascites - …

Gines P, Shrier RW. NEJM 2009
Decompensation: a “hemodynamic” event
ACLF driven by aggravated systemic hemodynamic dysfunction

- Precipitating event
- Acute increase in arterial vasodilation and decrease in cardiac output
- Burst in compensatory endogenous vasoconstrictor systems
- Resistance to portal venous flow
- Aggravation of portal hypertension
- Regional arterial vasoconstriction

- Kidney
- Brain
- Liver
- Adrenal gland
  - Hepatoadrenal syndrome
  - Encephalopathy
  - Liver failure
  - HRS

Sen S et al. Liver Int 2002
Decompensation: a “hemodynamic” event

The peripheral arterial vasodilation theory REVISITED

- Progressive circulatory dysfunction does not parallels levels of endogenous vasoconstrictor systems
- Progression of renal dysfunction occurs without progression of circulatory dysfunction

→ not fully accountable for mechanisms underlying progression of decompensation

Bernardi M et al. J Hepatol 2015, in press
Decompensation: a “metabolic” event

The toxin theory

Liver failure

↓ synthesis
↓ metabolisation
↓ detoxification

Accumulation of (vasoactive) toxins

Albumin-bound
Water-soluble

Bile acids, bilirubin
Prostacyclins
Nitric oxide
Indol/Phenol-Metabolites
Toxic fatty acids
Ammonia
Lactate

Cerebral dysfunction
Circulatory dysfunction
Renal dysfunction
Immune dysfunction

Jalan R et al Blood Purif 2002
Laleman W et al. Aliment Pharmacol Ther 2006
Decompensation: a “metabolic” event

The toxin theory

Liver failure

↑ synthesis
↑ metabolism
↑ detoxification

Albumin dialysis

Cerebral dysfunction
Circulatory dysfunction
Renal dysfunction
Immune dysfunction

Banares R et al. MARS RELIEF Hepatology 2013
Kribben A et al. HELIOS. Gastroenterology 2012
1. MARS: Molecular Adsorbent Recirculating System (Gambro)
Blood is perfused through a specific membrane dialyzer that uses albumin as **Molecular Adsorbent** that is **Recycled** in a Dialysis/Sorbent System (MARS)
Decompensation: a “metabolic” event

The toxin theory REVISITED

the classical ‘Chicken or the egg’-dilemma
Pathogenesis: contemporary perspective
Sepsis & MODS (multiple organ dysfunction syndrome)

- a vicious cycle of perpetuated inflammation and spread from one compartment to another -

Spilling over of inflammatory mediators induce tissue injury in different organs with further aggravation hereof, leading to finally MODS
Sepsis & MODS

Proof of concept: excessive inflammation and MODS
“Core” factor: excessive systemic inflammation
Balanced immune function
Resistance
Tolerance

Cirrhosis-associated immune dysfunction

Bacterial translocation
Decreased “effective” albumin concentration
Balanced immune function
Resistance
Tolerance

Cirrhosis-associated
immune dysfunction

Bacterial translocation
Decreased “effective” albumin concentration
Bacterial translocation: the instigator to ACLF

BT parallels severity of liver disease

Wiest R. J Hepatol 2014

Cirera I, Rodes J et al. J Hepatol 2001
Bacterial translocation: the instigator to ACLF

- BT parallels severity of liver disease

- Macrophage activation parallels severity of liver disease & impacts on prognosis

Cirera I, Rodes J et al. J Hepatol 2001

Waidmann O et al. J Hepatol 2013
White cell count and CRP correlate with increasing severity of ACLF

Leukocyte count (x10^9 cells)

C-reactive protein (mg/L)

* P < 0.05 vs no ACLF
** P < 0.001 vs no ACLF

Moreau R et al. CANONIC-trial. Gastroenterology 2012
Balanced immune function
Resistance
Tolerance

Cirrhosis-associated immune dysfunction

Bacterial translocation
Decreased "effective" albumin concentration
Immune hepatic surveillance (RES)

**cirrhosis**

- ↑ Intestinal permeability
  - Intestinal bacterial dysbiosis
  - Bacterial translocation

- ↑ PAMPs
  - TLR, NLR ...

- Infectious injury

- Hepatocellular damage/inflammation

- ↑ DAMPs
  - TLR, NLR ...

- Non-infectious injury

The stage for ACLF is set during cirrhosis progression
Early cirrhosis

↑ Intestinal permeability
Intestinal bacterial dysbiosis
Bacterial translocation

Infectious injury

TLR, NLR ...

Hepatocellular damage/inflammation

Non-infectious injury

TLR, NLR ...

Immune hepatic surveillance
(RE, innate, adaptive)

RESISTANCE
“search & destroy”

Shape immune response and elimination of bacteria and infected cells

IL-1β, IL-6, TNF-α,
CCL2, ...

TOLERANCE
“live & let live”

Damp inappropriate immune responses (“immuno-pathology”)

IL-10, IL1RA, sTNF-R
HLA-DR

The stage for ACLF is set during cirrhosis progression
Evolving cirrhosis

↑ Intestinal permeability
Intestinal bacterial dysbiosis
Bacterial translocation

Hepatocellular damage/inflammation

Infectious injury

Non-infectious injury

TLR, NLR ...

Immune hepatic surveillance
(RES, innate, adaptive)

shunting

Systemic inflammation
Activated circulating immune cells

Cirrhosis “primes” the systemic immune system
Infectious injury

Non-infectious injury

↑ Intestinal permeability
Intestinal bacterial dysbiosis
Bacterial translocation

Hepatocellular damage/inflammation

Infectious injury

Non-infectious injury

TLR, NLR ...

Overwhelmed Immune hepatic surveillance

Spill-over & more shunting

Systemic **excessive** inflammation
Activated circulating immune cells

Gene activation
Expression of surface molecules of activation
(cytokine receptors, adhesion molecules)
Cytokines and growth factors production
(pro-inflammatory lymphokines and monokines)
Systemic inflammation in healthy individual

- Bacterial challenge
- Dynamic homeostatic variability
- Immunodeficiency

Adequate - activation

Hyper -

Coordination in health

Recognition and effective effector response

Courtesy of Agustin Albillos
Albillos A et al. J Hepatol 2014
Cirrhosis-associated immune dysfunction: Compensated cirrhotic patient

- Gut barrier damage → translocation
- Protracted subclinical sterile inflammation
- Bacterial translocation
- Cirrhosis-associated immune dysfunction:
  - Compensated cirrhotic patient

Hyper-activation

Adequate-activation

Systemic inflammation

Recognition and effective effector response

Immunodeficiency

Coordination in health

Health

Compensated

Decompensated

ACLF

Cirrhosis progression

Time

Bacterial translocation

Courtesy of Agustin Albillos
Albillos A et al. J Hepatol 2014
Gut barrier damage → translocation

Bacterial translocation

Predominant “pro-inflammatory” CAID

Cirrhosis-associated immune dysfunction:
Decompensated cirrhotic patient

Systemic inflammation

Recognition and effective effector response

Immunodeficiency

Dissociation in decompensated cirrhosis

Dynamic homeostatic variability

Bacterial infection threshold?

Coordination in health

Adequate - activation

Hyper -

Health

Compensated

Decompensated

Cirrhosis progression

ACLF

Time

Bacterial translocation

Courtesy of Agustin Albillos

Albillos A et al. J Hepatol 2014
Cirrhosis-associated immune dysfunction:

ACLF = immunoparalysis

Gut barrier damage → translocation

Cirrhosis-associated immune dysfunction:

ACLF = immunoparalysis

Courtesy of Agustin Albillos

Albillos A et al. J Hepatol 2014
Cirrhosis-associated immune dysfunction:
ACLF = immunoparalysis

Predominant “immunodeficient” CAID
Balanced immune function
Resistance
Tolerance

Cirrhosis-associated immune dysfunction

Bacterial translocation
Decreased “effective” albumin concentration
“Effective” albumin concentration is reduced in ACLF  
Circulating albumin is quantitatively & qualitatively reduced in cirrhosis

**Functional impact**  
electron paramagnetic resonance spectroscopy

**Prognostic impact**  
Ischemia Modified Albumin/albumin Ratio

- IMAR < 0.02
- IMAR > 0.02

Jalan R et al. Hepatology 2009  
Domenicali M et al Hepatology 2014
“Effective” albumin concentration, $\text{PGE}_2$ & cirrhosis associated immune dysfunction

“Effective” albumin concentration, PGE$_2$ & cirrhosis associated immune dysfunction: exploiting the paradigm

Liver failure

“effective” albumin concentration

Bioavailability of PGE2

Macrophage and monocyte function

HSA 20%

Albumin dialysis

O’Brien AJ et al. Nat Medicine 2014 INFECIR-2 trial, in progress
Clinical picture: clinical trade-off of systemic inflammation
The Systemic Inflammation-hypothesis in evolving cirrhosis

- **Compensated Cirrhosis**
  - Moderate BT
  - Moderate SAV compensated by increased CO
  - No effective hypovolemia
  - No organ dysfunction
  - No organ failure

- **Early Decompensated Cirrhosis¹**
  - Significant BT
  - Significant SAV, no further increase in CO
  - Significant effective hypovolemia
  - Organ dysfunction
  - No organ failure

- ** Decompensated Cirrhosis²**
  - Severe BT
  - Severe SAV, decreased CO
  - Severe effective hypovolemia
  - Organ dysfunction
  - Renal failure

- **Acute Increase in Systemic Inflammation**
  - Acute bacterial infection
  - Acute "sterile hepatic inflammation"
  - Severe burst of BT

  - Severe impairment of systemic hemodynamics and cardiac function
  - Organ perfusion

  - Severe organ inflammation and oxidative stress
  - Cell necrosis and apoptosis

  - Microvascular damage

  - Organ failures

  - Acute-on-Chronic Liver Failure
“Peripheral arterial vasodilation” meets “systemic inflammation” theory

Bernardi M et al. J Hepatol 2015,
# Clinical features

## Table 1. Characteristics of patients with or without ACLF.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No ACLF* (N = 871)</th>
<th>ACLF (N = 417)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>58.1 ± 12.3</td>
<td>55.8 ± 11.7</td>
<td>0.0011</td>
</tr>
<tr>
<td>Male sex</td>
<td>551 (63.3)</td>
<td>267 (64.0)</td>
<td>0.7887</td>
</tr>
<tr>
<td>Ascites</td>
<td>533 (61.4)</td>
<td>289 (60.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>84.8 ± 11.9</td>
<td>78.4 ± 13.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cause of cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>398 (48.5)</td>
<td>233 (58.4)</td>
<td>0.0011</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>182 (22.2)</td>
<td>59 (14.8)</td>
<td>0.0024</td>
</tr>
<tr>
<td>Alcohol plus hepatitis C virus</td>
<td>76 (9.3)</td>
<td>37 (9.3)</td>
<td>0.9927</td>
</tr>
<tr>
<td>Potential precipitating events of ACLF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial infection</td>
<td>218 (25.2)</td>
<td>160 (39.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>99 (15.6)</td>
<td>74 (17.8)</td>
<td>0.3505</td>
</tr>
<tr>
<td>Active alcoholism within the last 3 months*</td>
<td>115 (13.9)</td>
<td>89 (22.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other precipitating event*</td>
<td>31 (3.8)</td>
<td>38 (9.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No precipitating event*</td>
<td>483 (64.8)</td>
<td>124 (34.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>More than one precipitating event*</td>
<td>41 (28.7)</td>
<td>25 (29.8)</td>
<td>0.8613</td>
</tr>
</tbody>
</table>

### Organ failures

<table>
<thead>
<tr>
<th>Failure</th>
<th>No ACLF* (N = 871)</th>
<th>ACLF (N = 417)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>51 (7.9)</td>
<td>156 (39.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Kidney</td>
<td>0 (0)</td>
<td>196 (49.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebral</td>
<td>13 (2.0)</td>
<td>87 (22.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coagulation</td>
<td>14 (2.2)</td>
<td>122 (31.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Circulation</td>
<td>10 (1.6)</td>
<td>89 (22.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lungs</td>
<td>3 (0.5)</td>
<td>50 (12.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Kidney dysfunction*</td>
<td>68 (7.8)</td>
<td>69 (16.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mild-to-moderate hepatic encephalopathy*</td>
<td>221 (25.4)</td>
<td>173 (41.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Laboratory data

<table>
<thead>
<tr>
<th>Test</th>
<th>No ACLF* (N = 871)</th>
<th>ACLF (N = 417)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>32 ± 6</td>
<td>28 ± 5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelet count (x10⁹/L)</td>
<td>110 ± 75</td>
<td>95 ± 71</td>
<td>0.0011</td>
</tr>
<tr>
<td>Serum bilirubin (mg/dl)</td>
<td>4.3 ± 5.0</td>
<td>11.7 ± 11.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>1.5 ± 0.4</td>
<td>2.1 ± 0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L)</td>
<td>54 ± 130</td>
<td>72 ± 126</td>
<td>0.0326</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/L)</td>
<td>90 ± 141</td>
<td>198 ± 716</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(\gamma)-Glutamyltransferase (U/L)</td>
<td>174 ± 298</td>
<td>130 ± 158</td>
<td>0.0019</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.9 ± 0.3</td>
<td>2.0 ± 1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum sodium (mmol/L)</td>
<td>135.7 ± 5.3</td>
<td>134.5 ± 6.6</td>
<td>0.0013</td>
</tr>
</tbody>
</table>
## Precipitating events in CANONIC

Table 1. Characteristics of patients with or without ACLF.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No ACLF&lt;sup&gt;a&lt;/sup&gt; (N = 871)</th>
<th>ACLF (N = 417)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>58.1 ± 12.3</td>
<td>55.8 ± 11.7</td>
<td>0.0011</td>
</tr>
<tr>
<td>Male sex</td>
<td>551 (63.3)</td>
<td>267 (64.0)</td>
<td>0.7887</td>
</tr>
<tr>
<td>Ascites</td>
<td>533 (61.4)</td>
<td>289 (80.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>84.8 ± 11.9</td>
<td>78.4 ± 13.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cause of cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>398 (48.5)</td>
<td>233 (58.4)</td>
<td>0.0011</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>182 (22.2)</td>
<td>59 (14.8)</td>
<td>0.0024</td>
</tr>
<tr>
<td>Alcohol plus hepatitis C virus</td>
<td>76 (9.3)</td>
<td>37 (9.3)</td>
<td>0.9927</td>
</tr>
<tr>
<td>Potential precipitating events of ACLF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial infection</td>
<td>218 (25.2)</td>
<td>160 (39.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>99 (15.6)</td>
<td>74 (17.8)</td>
<td>0.3505</td>
</tr>
<tr>
<td>Active alcoholism within the last 3 months&lt;sup&gt;b&lt;/sup&gt;</td>
<td>115 (13.9)</td>
<td>89 (22.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other precipitating event&lt;sup&gt;c&lt;/sup&gt;</td>
<td>31 (3.8)</td>
<td>38 (9.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No precipitating event&lt;sup&gt;d&lt;/sup&gt;</td>
<td>483 (64.8)</td>
<td>124 (43.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>More than one precipitating event&lt;sup&gt;e&lt;/sup&gt;</td>
<td>41 (28.7)</td>
<td>25 (29.8)</td>
<td>0.8613</td>
</tr>
</tbody>
</table>

40% bacterial infection
23% active alcoholism
30% more than one
43% no precipitating event

Jalan et al. J Hepatol 2015
Infectious & non-infectious events precipitate systemic inflammation in ACLF

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

* 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

Moreau R et al. CANONIC-trial. Gastroenterology 2012
Role of previous decompensation

Table 1. Characteristics of patients with or without ACLF.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No ACLF (N = 871)</th>
<th>ACLF (N = 417)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from first previous decompensation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No previous decompensation</td>
<td>237 (29.8)</td>
<td>98 (26.4)</td>
<td>0.2419</td>
</tr>
<tr>
<td>Less than 3 months</td>
<td>85 (10.7)</td>
<td>58 (15.6)</td>
<td></td>
</tr>
<tr>
<td>From 3 to 12 months</td>
<td>139 (17.5)</td>
<td>62 (16.7)</td>
<td>0.0967</td>
</tr>
<tr>
<td>More than 12 months</td>
<td>334 (42.0)</td>
<td>153 (41.2)</td>
<td></td>
</tr>
</tbody>
</table>

Moreau et al. Gastroenterology 2013

Jalan et al. J Hepatol 2015
Dynamic clinical course of ACLF

Final ACLF grade was already defined at days 3–7 in 81% patients.

<table>
<thead>
<tr>
<th></th>
<th>Initial ACLF grade</th>
<th>d3-7 ACLF grade</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUROC (95% CI)</td>
<td>AUROC (95% CI)</td>
<td></td>
</tr>
<tr>
<td>28-day mortality</td>
<td>0.6520 (0.5944, 0.7096)</td>
<td>0.8492 (0.8049, 0.8935)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>0.6218 (0.5673, 0.6763)</td>
<td>0.8091 (0.7637, 0.8545)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Aggravated systemic inflammation escalates the portal hypertensive syndrome

<table>
<thead>
<tr>
<th></th>
<th>Stable cirrhosis (n = 27)</th>
<th>Acute decompensation (n = 14)</th>
<th>ACLF (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White cell count (x10^9/L)</td>
<td>5.7 (4.9–6.8)</td>
<td>8.9 (4.7–13.7)††</td>
<td>11.7 (7.2–22.1)‡‡</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>7.8 (5.3–13.1)††</td>
<td>13.5 (9.1–41.2)††</td>
<td>41.1 (17–103)††</td>
</tr>
<tr>
<td>SIRS†</td>
<td>0 (0–1)</td>
<td>1 (0–2)††</td>
<td>2 (1–3)‡‡</td>
</tr>
<tr>
<td>TNF-R1 (ng/ml)</td>
<td>2.4 (1.1–3.9)††</td>
<td>2.9 (1.3–5.4)††</td>
<td>7.3 (3–27)††</td>
</tr>
<tr>
<td>TNF-R2 (ng/ml)</td>
<td>7.6 (2.5–5.5)††</td>
<td>9 (3.4–13.5)††</td>
<td>21.0 (10–45)††</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>3.9 (8–31.1)†</td>
<td>5.4 (3–43.3)††</td>
<td>43 (23–103)‡‡</td>
</tr>
<tr>
<td>IL-8 (pg/ml)</td>
<td>13 (3–17.9)†</td>
<td>27 (5–37)††</td>
<td>45 (3–115)‡‡</td>
</tr>
<tr>
<td>IL-10 (pg/ml)</td>
<td>1.9 (0.3–17)†</td>
<td>11 (3–19)††</td>
<td>32 (3–313)††</td>
</tr>
<tr>
<td>MDA (µM)</td>
<td>2.1 (1–3)</td>
<td>2.1 (1–3)</td>
<td>6 (3–12)††</td>
</tr>
<tr>
<td>Nitrate (µM)</td>
<td>32 (3–40)</td>
<td>53 (23–99)††</td>
<td>78 (15–170)‡‡</td>
</tr>
<tr>
<td>Nitrite (µM)</td>
<td>0.9 (2–9)</td>
<td>2.1 (1–9)††</td>
<td>5.3 (0–19)‡‡</td>
</tr>
</tbody>
</table>
Hepatic encephalopathy in ACLF is distinct clinically, prognostically and pathophysiologically

Romero-Gomez M et al. J Hepatol 2015
Odeh A et al. Liv International 2004
Cordoba J et al. J Hepatol 2014
The gut-liver-kidney axis
Systemic inflammation induces AKI in cirrhosis via TLR4

Shah N et al. J Hepatol 2012
Shah N et al Liver Int 2012
Prognostic scores
CLIF-C AD Score

CLIF-C AD score =

\[10 \times \left(0.03 \times \text{Age} + 0.66 \times \ln(\text{Creatinine}) + 1.71 \times \ln(\text{INR}) + 0.88 \times \ln(\text{WBC}) - 0.05 \times \text{Sodium} + 8\] \]

Age in years; Creatinine in mg/dL; WBC (white blood count) in \(10^9\) cells/L; Sodium in mmol/L.

Fig. 3. Predictive ability of CLIF-C AD score for 90-day mortality as compared to MELD, MELD-Na and Child-Pugh (CP) score.
CLIF-C ACLFs = 10 × [0.33 × CLIF-OFs + 0.04 × Age + 0.63 × ln(WBC count) − 2]

Fig. 3. Accuracy of the CLIF-C ACLFs as compared to that of MELDs, MELD-Nas and CPs in predicting 28-day mortality of the CANONIC patients with ACLF. Comparison of the area under the ROC curves (AUROCs) estimated for each score. The CLIF-C ACLFs showed a significantly higher predictive ability in comparison with all the other scores. (This figure appears in colour on the web.)

Fig. 4. Accuracy of the CLIF-C ACLFs as compared to that of MELDs, MELD-Nas, and CPs in predicting 90-day mortality of the CANONIC patients with ACLF. Comparison of the area under the ROC curves (AUROCs) estimated for each score. The CLIF-C ACLFs showed a significantly higher predictive ability in comparison with all the other scores. (This figure appears in colour on the web.)
Scores: via www or app
Use of CLIF-C scores

Admission of cirrhotic patient with acute decompensation

Assess CLIF-C OF score for diagnosis of ACLF

ACLX present

ACLX absent

CLIF-C ACLF score

CLIF-C AD score

High risk: CLIF-C ADs ≥60
3-month mortality >30%

Intermediate risk: CLIF-C ADs 46-59
3-month mortality 2-30%

Low risk: CLIF-C ADs ≤45
3-month mortality <2%

Jalan et al. J Hepatol 2015
Management of ACLF
Management of ACLF by HBV

- At present, there is no specific therapy for ACLF aside from antiviral therapy in patients with ACLF due to reactivation of HBV infection.

- Administration of nucleoside analogues (tenofovir, entecavir, lamivudine) improves liver function and decreases mortality in patients with ACLF due to HBV infection. Treatment should be started as early as possible.

Garg et al. Hepatology 2011
General management of ACLF

- Treatment of ACLF should be based on organ support and management of associated complications.

- Patients should be treated in intermediate care or intensive care settings. Organ function, particularly, liver, kidney, brain, lung, coagulation, and circulation should be monitored frequently and carefully throughout hospitalization, as ACLF is a dynamic condition.

- However, monitoring and management should be individualized according to specific circumstances, mainly patients’ age and comorbidities.
Early identification and treatment of precipitating factors of ACLF, particularly bacterial infections, halts the progression of the syndrome.

However, in some patients ACLF progresses despite treatment of precipitating factors.

Fernandez et al. Gut 2017
Infection & ACLF

Rate of infection during follow-up

- AD: 18.2%
- ACLF-1: 37.6%
- ACLF-2: 47.4%
- ACLF-3: 81.5%

P-value < 0.001

Probability of infection

P-value < 0.001
Antibiotics administration (NORFLOCIR)

**Cumulative Incidence of Death**

<table>
<thead>
<tr>
<th>Months</th>
<th>Placebo N=147</th>
<th>Norfloxacin N=144</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Child C patients
- Placebo
- Norfloxacin

**SHR* and 95% CI**

| Unadjusted | 0.586 | 0.346 to 0.992 | 0.0467 |
| Adjusted** | 0.575 | 0.338 to 0.979 | 0.0415 |

*Fine & Gray model. **For nonselective β-blockers and corticosteroids

Moreau et al. EASL 2017
Long-term albumin administration (ANSWER)

N= 431 cirhosis and uncomplicated ascites, all received standard medical treatment with anti-mineralocorticoids (at least 200 mg/day) and furosemide (at least 25 mg/day).

albumin 40 g twice a week for the first 2 weeks, and thereafter 40 g per week

<table>
<thead>
<tr>
<th>Months</th>
<th>N at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>SMT 213, SMT + HA 218</td>
</tr>
<tr>
<td>3</td>
<td>158, 182</td>
</tr>
<tr>
<td>6</td>
<td>110, 153</td>
</tr>
<tr>
<td>9</td>
<td>90, 135</td>
</tr>
<tr>
<td>12</td>
<td>76, 121</td>
</tr>
<tr>
<td>15</td>
<td>65, 109</td>
</tr>
<tr>
<td>18</td>
<td>28, 43</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hazard Ratio (HA+SMT vs SMT)</th>
<th>Log-rank P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.62 (95% CI 0.40-0.95) (-38%)</td>
<td>0.0285</td>
</tr>
</tbody>
</table>

Caraceni/Bernardi et al. EASL 2017
Long-term albumin administration (ANSWER)

Table. Secondary Outcomes Favoring Albumin Over Standard Medical Treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Incidence Rate Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>0.65</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Paracentesis</td>
<td>0.46</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Refractory ascites</td>
<td>0.54</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Spontaneous bacterial peritonitis (SBP)</td>
<td>0.32</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Non-SBP bacterial infection</td>
<td>0.70</td>
<td>.0045</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>0.50</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hepatorenal syndrome, type 1</td>
<td>0.38</td>
<td>.0039</td>
</tr>
<tr>
<td>Hepatic encephalopathy, grades III and IV</td>
<td>0.48</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Hazard Ratio (HA+SMT vs SMT) | Log-rank P value
0.62 (95% CI 0.40-0.95)     | 0.0285

Caraceni/Bernardi et al. EASL 2017
Liver transplantation

Liver transplantation is a very effective therapy for ACLF in selected patients because it improves survival compared to standard medical therapy.

A major issue for liver transplantation is high short-term mortality of ACLF. Therefore, early referral to transplant centers for immediate evaluation for liver transplantation is crucial.

Gustot et al. Hepatology 2015
Artru et al. J Hepatol 2017
Futility of care

In patients with 4 or more organ failures after one week of adequate intensive treatment, withdrawal of on-going intensive care support should be considered. These patients should probably not be considered candidates for liver transplantation due to very high mortality rate.

Table 3. Number of Organ Failures (OFs) and CLIF-C ACLFs in Patients With ACLF-3 at Days 3-7 After ACLF-3 Diagnosis*

<table>
<thead>
<tr>
<th>No. of OFs at 3-7 Days</th>
<th>28-Day Tx-Free Mortality (%)</th>
<th>90-Day Tx-Free Mortality (%)</th>
<th>CLIF-C ACLFs at 3-7 Days</th>
<th>28-Day Tx-Free Mortality (%)</th>
<th>90-Day Tx-Free Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95% CI</td>
<td>95% CI</td>
<td>95% CI</td>
<td>95% CI</td>
<td>95% CI</td>
</tr>
<tr>
<td>0</td>
<td>1/7 (14.3; 2.6-51.3)</td>
<td>1/7 (14.3; 2.6-51.3)</td>
<td>&gt;20-30</td>
<td>0/1 (0)</td>
<td>0/1 (0)</td>
</tr>
<tr>
<td>1</td>
<td>0/7 (0%)</td>
<td>1/7 (14.3; 2.6-51.3)</td>
<td>&gt;30-40</td>
<td>1/4 (25.0; 4.6-69.9)</td>
<td>1/4 (25.0; 4.6-69.9)</td>
</tr>
<tr>
<td>2</td>
<td>7/12 (58.3; 32.0-80.7)</td>
<td>9/11 (81.8; 52.3-94.9)</td>
<td>&gt;40-50</td>
<td>1/11 (9.1; 1.6-37.7)</td>
<td>4/10 (40.0; 16.8-68.7)</td>
</tr>
<tr>
<td>3</td>
<td>9/17 (52.9; 31.0-73.8)</td>
<td>13/17 (76.5; 52.7-90.4)</td>
<td>&gt;50-60</td>
<td>11/18 (61.1; 38.6-79.7)</td>
<td>13/18 (72.2; 49.1-87.5)</td>
</tr>
<tr>
<td>4</td>
<td>9/10 (90.0; 59.6-98.2)</td>
<td>10/10 (100; 72.3-100)</td>
<td>&gt;60-70</td>
<td>11/14 (78.6; 52.4-92.4)</td>
<td>13/14 (92.9; 68.5-98.7)</td>
</tr>
<tr>
<td>5</td>
<td>10/10 (100; 72.3-100)</td>
<td>10/10 (100; 72.3-100)</td>
<td>&gt;70-80</td>
<td>12/12 (100; 75.8-100)</td>
<td>12/12 (100; 75.8-100)</td>
</tr>
<tr>
<td>6</td>
<td>5/5 (100; 56.6-100)</td>
<td>5/5 (100; 56.6-100)</td>
<td>&gt;80-90</td>
<td>3/3 (100; 43.9-100)</td>
<td>3/3 (100; 43.9-100)</td>
</tr>
<tr>
<td>Total</td>
<td>41/68 (60.3; 48.4-71.1)</td>
<td>49/67 (73.1; 61.5-82.3)</td>
<td>Total</td>
<td>39/63 (61.9; 50.0-72.9)</td>
<td>46/62 (74.2; 62.1-83.5)</td>
</tr>
</tbody>
</table>

*Relationships to 28- and 90-day transplant (tx)-free mortality.

Gustot et al. Hepatology 2015
Potential future therapies for ACLF
A number of therapies for ACLF are under investigation. To date, the most promising appears to be the administration of G-CSF. However, more information is needed before this treatment could be recommended in ACLF patients.

Garg et al. Gastroenterology 2012
Fractioned Plasma-Separation/Absorption or Plasma-exchange

Plasmapheresis in ALF

EFFECT OF PLASMA EXCHANGE (PE)* ON SYSTEMIC INFLAMMATORY MARKERS AND LIVER AND RENAL FUNCTION. PILOT STUDY (10 Patients)

<table>
<thead>
<tr>
<th></th>
<th>Pre-PE</th>
<th>Post-PE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>WCC (\times 10^9)</td>
<td>11.4±10.2</td>
<td>6.4±6.4</td>
<td>0.005</td>
</tr>
<tr>
<td>PRC (mg/dL)</td>
<td>3.04±1.75</td>
<td>1.87±1.23</td>
<td>0.07</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>115±59</td>
<td>74±13</td>
<td>NS</td>
</tr>
<tr>
<td>TNF-alfa (pg/mL)</td>
<td>14±4</td>
<td>10±4</td>
<td>0.004</td>
</tr>
<tr>
<td>S. Creatinine (mg/dl)</td>
<td>1.8±1.0</td>
<td>1.1±0.4</td>
<td>0.01</td>
</tr>
<tr>
<td>S. Bilirubin (mg/dl)</td>
<td>23±7</td>
<td>12±3</td>
<td>0.07</td>
</tr>
<tr>
<td>Encephalopathy (%)</td>
<td>80%</td>
<td>50%</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Six PE sessions of 1.2 plasma volumes each during 11 days

Larsen FS et al J Hepatol 2016
Fernandez et al. unpublished
MARS (albumin dialysis)

Bañares et al. Hepatology 2013

Bañares et al. submitted
Ongoing studies for ACLF
Predicting Acute-on-Chronic Liver Failure in Cirrhosis (PREDICT) Study on behalf of the EASL-CLIF Consortium

International-European, investigator-initiated, multicenter, prospective, observational study

(1) critical period prior ACLF
(2) mechanisms and pathophysiology
(3) precipitating events of ACLF
Rationale for Stratification

Admission of cirrhotic patient with acute decompensation

Assess CLIF-C OF score for diagnosis of ACLF

Positive controls

ACLIF present

CLIF-C ACLF score

ACLIF absent

CLIF-C AD score

Study population

High risk: CLIF-C ADs ≥60 3-month mortality >30%

Intermediate risk: CLIF-C ADs 46-59 3-month mortality 2-30%

Low risk: CLIF-C ADs ≤45 3-month mortality <2%

Negative controls
Centers (54 centers)
Further just started studies

- ALIVER: The liver dialysis machine DIALIVE removes dysfunctional albumin and endotoxins, infuses fresh, functional albumin and specifically targets systemic inflammation using commercially available CE-marked filters in one unit. Existing liver dialysis machines do not restore albumin function, have only a limited effect on systemic inflammation and do not improve survival rates.

- CARBALIVE: Nanoporous carbon adsorbent with tailored porosity (Yaq-001) as a new therapeutic for the treatment of liver cirrhosis and non-alcoholic fatty liver disease.

- LIVERHOPE: SIMVASTATIN AND RIFAXIMIN AS NEW THERAPY FOR PATIENTS WITH DECOMPENSATED CIRRHOSIS.
“Doctors are men who prescribe medicine about which they know little, to cure diseases of which they know less, in human beings of whom they know nothing”

(Voltaire, 1694-1778)