**SUPPLEMENTARY TABLE 1. General Characteristics of all patients**

| Parameter | n=249 |
|-----------|-------|
| **General Condition** | |
| Age [years] | 60 (31 - 82) |
| Sex [male / female] | 183 (73) / 66 (27) |
| Etiology of cirrhosis [alcohol / viral / other] | 185 (74) / 26 (11) / 38 (15) |
| BMI [kg/m²] | 25 (13 - 45) |
| **Baseline Scores** | |
| MELD§ | 10 (6 - 25) |
| Child-Pugh [A / B / C] | 97 (39) / 70 (28) / 82 (33) |
| Child-Pugh | 7 (5 - 12) |
| CLIF-C AD¥ | 49 (33 - 67) |
| **Baseline Laboratory** | |
| Hb [g/dl] | 12.4 (6.8 - 17.1) |
| WBC [G/l]† | 7 (1.8 - 23.3) |
| Platelets [G/l]‡ | 150 (29 - 647) |
| Sodium [mmol/l] | 137 (114 - 146) |
| Creatinine [mg/dl] | 0.9 (0.4 - 2.7) |
| Bilirubin [mg/dl]§ | 1 (0.1 - 12.7) |
| ALT [U/l]§ | 30 (7 - 311) |
| Albumin [g/l]§ | 32 (15 - 47) |
| INR§ | 1.3 (0.9 - 2.6) |
| **Baseline Clinical** | |
| Ascites [no / yes] | 128 (51) / 121 (49) |
| Esophageal Varices [no - grade I / grade II - III] | 193 (78) / 56 (22) |
| **Outcome** | |
| Mortality 1-year / overall | 39 (16) / 88 (35) |
| Fatal ACLF development 1-year / overall | 21 (8) / 52 (21) |
| Time to fatal ACLF development [months] | 17 (0 – 137) |
| Follow Up time [years] | 3 (0 - 15) |
| **Biomarkers** | |
| IL-1α [Undetectable / detectable] | 187 (75) / 62 (25) |
| Detectable [pg/ml] | 69.8 (8.5 – 1573.8) |
| IL-1β [Undetectable / detectable] | 172 (69) / 77 (31) |
| Detectable [pg/ml] | 73.8 (4.1 – 1180.5) |

Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; ALT, alanine transaminase; AP, alkaline phosphatase; BMI, body mass index; CLIF-C (European Foundation for the study of chronic liver failure consortium); Hb, hemoglobin; IL, interleukin; INR, international normalized ratio; MELD, Model for end-stage liver disease; WBC, white blood cells.

Data are expressed as median (range) or absolute frequency (percentage).

§Data available in 246 patients, †Data available in 245 patients, ¥Data available in 231 patients
**SUPPLEMENTARY TABLE 2.** ELISA kits and limits of detection

| Interleukin | Kit                                      | Range of detection (pg/ml) |
|-------------|------------------------------------------|----------------------------|
| IL-1α       | Human 1L-1alpha/IL1-1F DuoSet<sup>®</sup> ELISA (DY200-05) | 7.81 – 500                 |
| IL-1β       | Human IL-1beta/IL-1F2 DuoSet<sup>®</sup> ELISA (DY201)       | 3.91 – 250                 |

Abbreviations: IL, interleukin

**SUPPLEMENTARY TABLE 3.** Interleukin baseline levels stratified by time era and MELD.

| MELD ≤ 11 | 2002-2011 n=31 | 2012-2016 n=98 | p    |
|-----------|----------------|----------------|------|
| IL-1α     | 34.6±72.0      | 35.0±93.3      | 0.981|
| IL-1β     | 53.1±131.8     | 45.3±151.2     | 0.797|

| MELD > 11 | 2002-2011 n=44 | 2012-2016 n=77 | p    |
|-----------|----------------|----------------|------|
| IL-1α     | 95.4±267.4     | 48.9±129.4     | 0.210|
| IL-1β     | 100.3±218.7    | 80.3±183.1     | 0.361|

Abbreviations: MELD, model for end-stage liver disease.

**SUPPLEMENTARY TABLE 4.** Detailed cause mortality in Compensated and Recompensated cirrhosis

| Cause of death n(%) | All patients n=89 | Compensated n=30 | Recompensated n=59 |
|---------------------|-------------------|------------------|---------------------|
| ACLF                | 52 (58.5)         | 14 (46.6)        | 38 (64.4)*          |
| HCC                 | 5 (5.6)           | 2 (6.7)          | 3 (5.1)             |
| Other cancer        | 5 (5.6)           | 2 (6.7)          | 3 (5.1)             |
| Cardiovascular      | 13 (14.6)         | 6 (20.0)         | 7 (11.8)            |
| Unknown/Other       | 14 (15.7)         | 6 (20.0)         | 8 (13.6)            |

*p<0.05; Abbreviations: ACLF, acute-on-chronic liver failure; HCC, hepatocellular carcinoma.
SUPPLEMENTARY TABLE 5. Triggers of fatal ACLF

| Fatal ACLF trigger n(%) | All patients | Compensated | Recompensated |
|-------------------------|-------------|-------------|---------------|
|                         | n=52        | n=14        | n=38          |
| Infection               | 13 (25.0)   | 3 (21.5)    | 10 (26.3)     |
| Bleeding                | 6 (11.5)    | 1 (7.1)     | 5 (13.2)      |
| Unknown                 | 33 (63.5)   | 10 (71.4)   | 23 (60.5)     |

Abbreviations: ACLF, acute-on-chronic liver failure; HRS, hepatorenal syndrome

SUPPLEMENTARY TABLE 6. Interleukin baseline levels stratified by fatal ACLF development

| Interleukin level | Fatal ACLF development n=52 | No Fatal ACLF development n=197 |
|-------------------|-----------------------------|---------------------------------|
| IL-1α             |                             |                                 |
| [Undetectable / detectable] | 33 (63) / 19 (37) | 154 (78) / 43 (22) * |
| Detectable [pg/ml] | 117.2 (19.3 – 1573.8) | 45.6 (8.5 – 723.5) |
| IL-1β             |                             |                                 |
| [Undetectable / detectable] | 30 (58) / 22 (42) | 142 (72) / 55 (28) * |
| Detectable [pg/ml] | 191.9 (4.3 – 1036.1) | 53.7 (4.1 – 1180.5) * |

IL, interleukin, *if p<0.05
SUPPLEMENTARY TABLE 7. General characteristics and interleukin-1β levels and detection rate of the external cohort 1 admitted for recompensation of acute decompensation stratified by development of ACLF

| Parameter | no ACLF development | ACLF development |
|-----------|---------------------|------------------|
|           | n=32                | n=16             |
| **General Condition** | | |
| Age [years] | 58 (18-79) | 66 (29-80) |
| Sex [male / female] | 17 (53) / 15 (47) | 10 (63) / 6 (37) |
| Etiology of cirrhosis (alcohol / viral / other) | 17 (53) / 5 (16) / 10 (31) | 10 (63) / 2 (12) / 4 (25) |
| **Baseline Scores** | | |
| MELD | 9 (7-20) | 9 (6-26) |
| Child-Pugh [A / B / C] | 6 (19) / 24 (75) / 2 (6) | 2 (12.5) / 12 (75) / 2 (12.5) |
| Child-Pugh | 8 (5-12) | 8 (6-11) |
| CLIF-C AD | 45 (23-65) | 50 (33-72)* |
| **Baseline Laboratory** | | |
| Hb [g/dl] | 10.2 (7.8-13.3) | 10.1 (8.2-15.9) |
| WBC [G/l] | 5.7 (2.4-15.6) | 5.5 (3.7-13.7) |
| Platelets [G/l] | 118 (46-209) | 145 (39-234) |
| Sodium [mmol/l] | 139 (130-145) | 137 (121-143) |
| Creatinine [mg/dl] | 1.0 (0.5-2.6) | 1.0 (0.6-7.6) |
| Bilirubin [mg/dl] | 0.9 (0.2-4.4) | 0.9 (0.3-4.8) |
| ALT [UI/l] | 27 (14-121) | 24 (6-44) |
| Albumin [g/l] | 33.4 (17.2-40.0) | 28.0 (17.5-40.8) |
| INR | 1.1 (1.0-1.5) | 1.1 (1.0-1.4) |
| **Bio-marker** | | |
| IL-1β [Undetectable / detectable] | 21 (66) / 11 (34) | 5 (31) / 11 (69)* |
| Detectable [pg/ml] | 0 (0-43.7) | 1.9 (0-2.9)* |

Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; ALT, alanine transaminase; CLIF-C (European Foundation for the study of chronic liver failure consortium); Hb, hemoglobin; IL, interleukin; INR, international normalized ratio; MELD, Model for end-stage liver disease; WBC, white blood cells.

Data are expressed as median (range) or absolute frequency (percentage).

*p<0.05
### SUPPLEMENTARY TABLE 8. General characteristics and interleukin baseline levels of the external cohort 2 with acute decompensation stratified by presence of ACLF at time of admission

| Parameter                          | No ACLF (N = 101) | ACLF (N = 178) |
|------------------------------------|-------------------|----------------|
| **General condition**              |                   |                |
| Age (years)                        | 59 ± 12           | 57 ± 11*       |
| Sex [male / female]                | 58 (57) / 43 (43) | 114 (64) / 64 (36)* |
| Etiology of cirrhosis (alcohol / viral / other) | 40 (40) / 36 (36) / 25 (24) | 100 (56) / 46 (26) / 32 (18)* |
| **Scores**                         |                   |                |
| Child-Pugh                         | 9 ± 7             | 11 ± 2***      |
| MELD                               | 16 ± 6            | 27 ± 7***      |
| **Baseline Laboratory**            |                   |                |
| WBC (x10⁹/L)                       | 6.2 ± 3.1         | 9.7 ± 7.4**    |
| Platelet count (x10⁹/L)            | 90.9 ± 47.9       | 95.3 ± 65.6    |
| Serum creatinine (mg/dL)           | 1.2 ± 0.6         | 2.4 ± 1.6***   |
| Serum bilirubin (mg/dL)            | 5.1 ± 7.3         | 11.2 ± 11.4*** |
| INR                                | 1.6 ± 0.5         | 2.0 ± 0.9***   |
| Albumin (g/dL)                     | 2.8 ± 0.6         | 2.9 ± 0.7      |
| **Interleukins**                   |                   |                |
| IL-1α [Undetectable / detectable]  | 66 (67) / 33 (33) | 68 (40) / 108 (60)** |
| IL-1β [Undetectable / detectable]  | 91 (92) / 8 (8)   | 150 (84) / 28 (16)** |

Abbreviations: ACLF, acute-on-chronic liver failure at admission; no ACLF, no acute-on-chronic liver failure at admission; IL, interleukin; INR, international normalized ratio; MELD, model for end-stage liver disease; WBC, white blood cells.

Data expressed as mean ± SEM or absolute frequency (percentage).

| Data available in | Data available in |
|-------------------|-------------------|
| 275 patients      | 277 patients      |

IL-1α and IL-1β data show absolute number (percentage) of patients with detectable and undetectable levels

*** if \( p < 0.001 \), ** if \( p < 0.01 \), * if \( p < 0.05 \)
Supplementary Material 1.

LPS administration is used to study organ-specific (e.g. neural/renal inflammation), as well as systemic inflammatory response and therefore is well characterized in rodents without cirrhosis. Thus, studies investigate either the acute or long-term response to LPS. Increased levels of IL-1α and IL-1β are detected in liver tissue of rats 30 minutes after injection of LPS (Sang et al. Archives of Biochemistry and Biophysics; 1999) and a peak in serum levels is reached 2-6 hours after injection (Dzhalilova, J Inflamm Res, 2019; Chensue et al. American Journal of Pathology, 1991). Interestingly, IL-1α and IL-1β expression returns to baseline 18 hours after single LPS administration in hepatic sinusoidal macrophages, as well as 24 hours after LPS in serum. Several studies indicate a fast recovery of the LPS-induced inflammatory state (Bozadas et al. Folia Neuropathol, 2019) when LPS was administered as a single dose. Nevertheless, the extent of the inflammatory response as well as the survival rates are directly associated with the chosen dose of LPS (Thomas, Peptides, 2014; Ranneh et al. Arch Immunol Ther Exp, 2019).

Therefore, we investigated the short- and long-term effect of a sublethal dose of LPS to mimic AD and recompensation in cirrhosis. To our knowledge, this is the first study describing an acute (AD) as well as a chronic (recompensation) change in expression profile of Il-1α and Il-1β pathway after LPS stimulation in liver cirrhosis.
Supplementary Figure 1.

**A**

**IL-1α**

Patients at risk

| Year | 0   | 1   | 2   | 3   | 4   | 5   |
|------|-----|-----|-----|-----|-----|-----|
| 97   | 89  | 70  | 57  | 31  | 24  |     |
| 31   | 28  | 25  | 18  | 12  | 10  |     |
| 90   | 69  | 50  | 35  | 19  | 14  |     |
| 31   | 20  | 14  | 10  | 7   | 6   |     |

Years of follow up

p<0.001

**B**

**IL-1β**

Patients at risk

| Year | 0   | 1   | 2   | 3   | 4   | 5   |
|------|-----|-----|-----|-----|-----|-----|
| 95   | 89  | 74  | 61  | 34  | 27  |     |
| 33   | 28  | 21  | 14  | 9   | 7   |     |
| 77   | 58  | 43  | 30  | 16  | 12  |     |
| 44   | 31  | 21  | 15  | 10  | 8   |     |

Years of follow up

p<0.001
Supplementary Figure 2.

The AUROC for compensated fatal ACLF

| Source of the Curve | Sensitivity | Specificity |
|---------------------|-------------|-------------|
| Child-Pugh score    | 0.511       | 0.739       |
| MELD score          | 0.292       | 0.586       |
| MELD-Na score       | 0.022       | 0.687       |
| CLIF_C AD score     | 0.008       | 0.735       |
| IL-1α               | 0.691       | 0.533       |
| CLIF-C AD-IL-1α     | 0.007       | 0.739       |

Supplemental material

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Gut

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Supplementary Figure 3.

AUROC for recompensated

Source of the Curve
- Child-Pugh score
- MELD score
- MELD-Na score
- CLIF_AD score
- IL-1β
- CLIF_C AD + IL-1β
- Reference Line

| Parameter         | p     | AUC  | CI       |
|-------------------|-------|------|----------|
| fatal ACLF        |       |      |          |
| Child-Pugh score  | 0.150 | 0.582| 0.464-0.699|
| MELD              | 0.142 | 0.585| 0.481-0.689|
| MELD-Na score     | 0.012 | 0.645| 0.544-0.746|
| CLIF_AD score     | 0.002 | 0.681| 0.573-0.788|
| IL-1β             | 0.119 | 0.589| 0.474-0.704|
| CLIF-C AD-IL-1β   | 0.001 | 0.689| 0.584-0.794|
Supplementary Figure 4.

ACLF development

| Months | Patients at risk |
|--------|-----------------|
| 0      | 26              |
| 3      | 24              |
| 6      | 20              |
| 9      | 16              |
| 12     | 13              |
| 0      | 22              |
| 3      | 14              |
| 6      | 11              |
| 9      | 7               |
| 12     | 5               |

IL-1β detection
- undetectable
- detectable
- undetectable-censored
- detectable-censored