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The Intensive Care Unit (ICU) course and outcome in Acute-on-chronic liver failure are comparable to other ICU populations

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List of abbreviations

ACLF	Acute-on-chronic liver failure
CRP	C-reactive protein
BMI	body mass index
LT	liver transplantation
CVVH	continuous veno-venous hemofiltration
IHD	intermittent hemodialysis

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Abstract:

Background and aims: Acute-on-chronic liver failure (ACLF) is characterized by acute decompensation of cirrhosis, development of organ failure and high short term mortality. It is unknown whether outcome in ACLF patients admitted to ICU with organ failure is different from other ICU populations. We compared the clinical course and host response in ICU patients with or without ACLF, matched for baseline severity of illness scores and characteristics.

Methods: From the large prospective EPaNIC randomized control trial database (n=4640), 133 patients were identified with cirrhosis of whom 71 fulfilled the CLIF criteria for ACLF. These patients were matched for type and severity of illness and demographics to 71 septic and 71 medical ICU patients from the same database without chronic liver disease. Clinical, biochemical and outcome parameters were compared in this cohort study of 213 patients. In a subset of 100 patients, day-1 serum cytokines were quantified.

Results: The outcome of ACLF, when compared to septic or medical ICU patients, matched for baseline parameters of illness severity was similar regarding length of ICU stay, development of new infections, organ failure and septic shock. In addition ICU, hospital and 90-day mortality were similar between the groups. C-reactive protein and platelet levels were lower in ACLF throughout the first week in ICU. Cytokines on day 1 including IL-10, IL-1 β , IL-6, and IL-8 were similarly elevated in ACLF and septic ICU patients and TNF- α levels were higher in ACLF.

Conclusion: ACLF patients admitted to the ICU showed comparable clinical and ICU outcomes compared to ICU patients without chronic liver disease with similar baseline severity of illness characteristics. This suggests that admission criteria to the ICU should not be different in ACLF compared to other populations.

Lay summary

Liver function may abruptly deteriorate in patients with chronic liver disease with cirrhosis which often results in these patients being admitted to an intensive care unit with organ failure.

Previous studies have indicated that this sudden deterioration, called acute-on-chronic liver failure (ACLF) is associated with very high mortality rates which often resulted in deferred ICU care because of a perception of futility

Our study now show that the ICU course and outcome are not different when patients with ACLF are compared to other ICU patients when matched for severity of illness suggesting that ACLF deserves the same ICU care given to other ICU populations

Introduction

Acute-on-chronic liver failure (ACLF) is a recently defined clinical entity characterized by acute deterioration of compensated or stable decompensated cirrhosis associated with organ failure and a high 28-day mortality (1-6). ACLF as an entity differs in its clinical presentation and prognosis from alcoholic hepatitis and decompensated cirrhosis without organ failure (4, 7). Also, the inflammatory response is more pronounced in ACLF compared to compensated or decompensated cirrhosis with preserved organ function (4). White blood cell counts and plasma pro-inflammatory cytokines and C-reactive protein (CRP) levels are higher in ACLF patients than in cirrhotic patients without ACLF (8-10). This excessive inflammatory response may be an important contributing factor in the development of organ failure and immune exhaustion which may predispose to the development of new infections especially in hospitalized individuals (1, 11).

Cirrhotic patients with organ failure admitted to the ICU have a high ICU and hospital mortality, ranging from 36 to 89%, depending on the type and number of organ failures (1, 12-15). These high mortality rates commonly impact on the decision not to admit these patients to the ICU, especially when not regarded eligible candidates for liver transplantation. However, it is still unknown whether the outcome of ACLF is in fact inferior, when compared to the outcome of patients without chronic liver disease admitted to the ICU with organ failure.

We hypothesized that ACLF patients, due to an altered host immune response and underlying cirrhosis, will have inferior outcomes when compared to an ICU population with organ failure without chronic liver disease. To test this hypothesis, we compared the clinical ICU course and outcome of patients with ACLF to patients without chronic liver disease, but with comparable baseline characteristics, including demographics, presence of comorbidities and clinical parameters of illness severity. As ACLF patients share similar clinical and biochemical characteristics with septic patients (8, 16), we first compared the clinical ICU outcome of ACLF patients to a non-ACLF mixed medical and surgical ICU

population with a diagnosis of sepsis upon admission to the intensive care. Secondly, as sepsis is also a frequent precipitating factor in ACLF (1, 3, 4, 10), potentially introducing bias, we subsequently compared the clinical ICU course and outcome of patients with ACLF to medical ICU patients suffering from non-hepatic organ failure, again matched for baseline characteristics and severity of illness scores, but also for diagnosis of sepsis on admission.

Materials and methods

Patient population

To compare the ICU outcome of patients with ACLF to other ICU patients with similar illness severity, we performed a posthoc secondary analysis of a large clinical database from the prospective, multicenter EPaNIC trial, which is a randomized controlled trial of heterogeneous adult ICU patients comparing early versus late administration of parenteral nutrition to supplement insufficient enteral nutrition (17). The design and results of the EPaNIC trial have been published earlier (17). Patients were admitted between August 2007 and November 2010 to a tertiary university hospital with liver transplantation facilities. From the original patient population (n=4640), 133 patients were identified with cirrhosis of which 71 fulfilled the CANONIC criteria for ACLF (4). Cirrhosis was diagnosed based on clinical, biochemical and ultrasonography or histological data. Acute decompensation was defined as development of upper gastrointestinal bleeding, overt ascites, new onset of hepatic encephalopathy and/or bacterial infection. Organ failure in the ACLF group was diagnosed using the CLIF-SOFA score, a modified SOFA score for critically ill cirrhotic patients, recently developed in a multi-center study (4).

First, we performed a propensity scored selection of the EPaNIC database, matching for baseline characteristics and severity of illness, in a subgroup of mixed surgical and medical patients with sepsis on admission, but without ACLF or chronic liver disease (Table 1). Propensity scores were obtained by logistic regression, with one-to-one nearest neighbor matching without replacement (18). For this matching, the following baseline characteristics were used: gender, age, BMI, nutritional risk score, pre-admission dialysis, malignancy, diabetes, APACHE II score on admission, and randomization to

early or late parenteral nutrition. This subgroup is further referred to as “septic ICU patients”. In a subset of 100 patients (50 ACLF and 50 septic ICU patients), baseline cytokine concentrations were determined in serum samples collected on day 1 following ICU admission (Supplemental Table 1 for patient characteristics). Secondly, to exclude possible bias due to the fact that 70% of the ACLF population also suffered from sepsis upon ICU admission, an additional comparator group was analyzed. For this analysis, we selected 71 patients from the EPaNIC study admitted to the medical ICU matched to the ACLF patient group for “sepsis on admission” and the other baseline risk factors described above with use of propensity scores. This subgroup is further referred to as “medical ICU patients”.

As the trial was designed and performed before the introduction of the new, more sensitive, sepsis definitions (19) the old definition of sepsis was (20) used which could have underestimated the number of sepsis patients. In order to exclude this possibility we reanalyzed our three groups using the new definition. We could confirm that all patients who met the old criteria did meet the new criteria. In addition, none of the patients who were classified as “non-septic” were diagnosed as having sepsis according to the new definition excluding the possibility of misclassification.

Statistical analysis

Data are presented as mean with standard deviation or median with interquartile ranges. Group comparisons were performed using parametric student t-test or Wilcoxon/Kruskal-Wallis or Pearson’s chi-squared testing where appropriate. Multivariable Cox proportional hazard analysis was performed to investigate parameters with the time-to-alive ICU discharge as the dependent variable. Data for patients who died were censored. Statistical analyses were performed using JMP® version 12 (SAS Institute, Inc, Cary, NC). Two-sided P-value ≤ 0.05 was considered statistical significant.

Cytokine measurements

Meso Scale Discovery V-plex assays (Gaithersburg, MD) were used to determine plasma cytokine (INF- γ , IL-1 beta, IL-6, IL-8, IL-10 and TNF- α) and chemokine (CCL-2, CCL-3 and CCL-13) levels. All measurements were performed in duplicate according to manufactures instructions.

Results

Clinical ICU outcome of patients with ACLF and non-ACLF patients with comparable baseline risk factors

Of the 71 patients diagnosed with ACLF, 8 (11%) had ACLF grade 1, 34 (48%) had ACLF grade 2 and 29 (41%) had ACLF grade 3 upon ICU admission. Of the 29 patients with ACLF grade 3, 14 patients had 3, 10 patients had 4, 4 patients had 5 and 1 patient had 6 failing organs. Median (IQR) serum albumin, sodium and INR on admission were respectively 27.2 (24.4 – 30.8) g/L, 136 (132.5 – 139,3) mmol/L and 4.3 (1.84 – 11.1). Fifty ACLF patients (70%) were diagnosed with sepsis on admission. Three patients with cirrhosis developed acute decompensation and ACLF following surgery: in two patients following cardiothoracic and in one patient following abdominal surgery. Of the 71 ACLF patients, 9 patients underwent liver transplantation within the time frame of 90 days (between 3 and 36 days after ICU admission).

The characteristics of the ACLF patients and the 71 matched patients with sepsis are shown in Table 1. The majority of the 71 septic patients were admitted after major surgery (48%) or due to a respiratory disease (21%). All 71 non-ACLF septic patients had an infection upon admission. ACLF patients clearly displayed higher admission bilirubin and higher maximum bilirubin during ICU stay compared to non-ACLF septic ICU patients, which resulted in higher SOFA scores (Table 1). Other baseline risk factors, including demographics, presence of other comorbidities and clinical parameters of illness severity were comparable between the two cohorts. Short-term outcome in ACLF patients appeared similar compared to the septic ICU patients (Table 2). Specifically, ACLF and the sepsis cohort were similar regarding duration of ICU and hospital stay, development of new ICU acquired infections, new organ

failure, new septic shock, and ICU, hospital and 90-day mortality. Also, the need for organ support, including mechanical ventilation, vasopressor and renal replacement therapy, was similar in both groups. Liver transplant free ICU and hospital mortality was also similar between ACLF and non-ACLF septic patients, whereas liver transplant free 90 days mortality tended to be higher in patients with ACLF (43% vs. 27%, $p=0.06$). Liver transplant free ICU and 90-day mortality in ACLF 1 was 0% (0/7) and 14% (1/7), in ACLF 2 19% (6/32) and 32% (10/31), and in ACLF 3 40% (10/25) and 62.5% (15/24), respectively. ACLF 3 patients with 3, 4, 5 or 6 organ failures had a LT free ICU and 90-day mortality of 45.5% (5/11) and 70% (7/10), 22.2% (2/9) and 66.6% (6/9), 50% (2/4) and 50% (2/4) and 100% (1/1) and 100% (1/1), respectively.

To exclude the possibility that sepsis induced bias in the comparison of outcome, we also compared the 71 ACLF patients to a medical ICU population. Seventy-one patients were matched for the same baseline risk factors as the septic group, however including the presence of sepsis on admission (70%) (Table 1). The majority of the latter group was admitted for a respiratory disease (42%) or gastro-intestinal or hepatic disease (28%). In the latter group none of the patients had chronic liver disease, 4 were admitted for acute liver failure (3 due to paracetamol and 1 due to Amanita ingestion). As in the septic patient population, the ACLF group had higher admission and maximum in-ICU bilirubin and hence higher SOFA scores, compared to the medical ICU group. Other baseline risk factors were comparable in both groups. This second comparison again demonstrated that the ICU outcome was not different between ACLF patients and non-ACLF patients with a similar severity of illness (Table 2). ACLF and medical ICU cohorts were similar regarding length of ICU and hospital stay, development of new infections, new onset organ failure or septic shock, as well as the need for organ support. In addition ICU, hospital and 90-day mortality were also comparable between these two groups.

A multivariate Cox proportional hazard analysis assessing the impact of ACLF on time-to-alive discharge from ICU, adjusted for baseline risk factors, indicated that APACHE II score and sepsis on admission was significantly associated with a lower likelihood of an early ICU discharge whereas the

diagnosis of ACLF was not (Table 3). For both comparisons similar results were found for likelihood of an early hospital discharge (data not shown). When those patients receiving a liver transplant within 90 days of their ICU admission were excluded from the analysis, ACLF was still not a determining factor for a liver transplant free time-to-alive discharge from the ICU or the hospital (data not shown). Also, when receiving a liver transplant was added to the model as an additional factor, it did not determine time-to-alive-discharge from the ICU or hospital (data not shown).

Immune response of patients with ACLF and non-ACLF patients with comparable baseline risk factors

The ACLF cohort had significantly higher bilirubin levels (Table 1), but lower CRP values and platelet counts compared to the two ICU cohorts throughout the first week in ICU (Figure 1). However, the white blood cell count, indicative of the inflammatory response, was similarly elevated in ACLF patients and non-ACLF patients (Figure 1).

In a subset of 50 ACLF patients and 50 matched non-ACLF septic patients, cytokines were quantified on day 1 following ICU admission (Supplementary Table 1). All quantified cytokines were comparable between ACLF and non-ACLF patient cohorts (Table 4). Only day 1 CCL13 serum concentration was significantly lower and TNF- α significantly higher in ACLF patients. Of note IL-8 and IL-6 levels were similarly elevated in both ACLF and non-ACLF groups.

As renal replacement therapy might have affected cytokine levels, we reanalyzed both patient groups excluding patients receiving renal replacement therapy (ACLF group: 2 CVVH; Septic group: 1 CVVH and 1 IHD). Serum cytokine measurements were similar before and after exclusion of dialysed patients.

Discussion

Patients with ACLF that develop organ failure have high short term mortality. However it is not known if the clinical course and mortality associated with ACLF is different from other ICU populations. In this study, using the CLIF criteria to select patients with ACLF, we demonstrated that the ICU

outcome in ACLF patients is similar compared to a propensity matched non-ACLF ICU population without chronic liver disease. Specifically we demonstrated that the length of ICU stay, the development of organ failure, new infections or septic shock, and need for organ support, as well as ICU and hospital mortality did not differ between matched populations.

Although ACLF as a clinical entity is not disputed by the major societies including the AASLD , EASL, APASL controversy still exist regarding an universal definition of this syndrome (2). In the United States ACLF is generally regarded as the manifestation of sepsis in cirrhosis, whereas in Asia emphasis is placed on the development of jaundice and encephalopathy before other signs of decompensation. According to the CLIF consortium and EASL, ACLF refers to acute hepatic decompensation in patients with cirrhosis often as a result of a precipitating (hepatic or extra-hepatic) event followed by the development of multi-organ failure.

During the disease course of cirrhosis, admission to the ICU is often required as a result of episodes of acute decompensation and progression to organ failure associated with impaired survival proportional to the type and number of failing organs. (21, 22). In the Canonic study, a multi-center prospective European study, a clear association was shown between increasing ACLF grade and 90-day mortality that ranged from 41% in ACLF-1, to 52% in ACLF-2 and 79% in ACLF-3 (4). Of specific note however only 31% of ACLF patients in the Canonic study were admitted to the ICU upon admission or at any time during their disease course (4).

Due to the poor prognosis associated with ACLF and the perception regarding futility of care, the initiation of organ support in the ICU is often questioned by intensive care physicians and hepatologists alike, especially in those patients not eligible for liver transplantation. However, we now demonstrate that ICU outcome in ACLF patients is similar compared to both septic and medical ICU patients with comparable admission disease severity scores. In addition our study demonstrated that

ACLF patients receiving maximal ICU and organ support had overall 90 day mortality rates of 40% which is lower than reported in the Canonic study.

Of considerable interest, although ACLF patients in our study had significantly higher bilirubin levels with consequently higher SOFA scores on admission, this did not impact the ICU outcome including the need and duration of organ support, length of ICU and hospital stay and ICU, hospital and 90-day mortality. In fact a multivariate Cox proportional hazard analysis showed that the APACHE II score and sepsis on admission were significantly associated with a lower likelihood of an early ICU discharge whereas the diagnosis of ACLF was not. This finding implies that the ICU course and survival of patients with ACLF is less determined by progressive liver dysfunction but rather by organ failure similar to other conditions admitted to the ICU. This also suggests that the development of ACLF may be, at least early in its course, reversible through the prevention of infection or the early recognition of sepsis before organ failure ensues (23-25).

Outside the context of ICU care, ACLF has been associated with features of important systemic inflammation (4, 26, 27). White blood cells, plasma levels of C-reactive protein and pro-inflammatory cytokines such as IL-6 and IL-8 are elevated and higher in ACLF compared to cirrhotic patients without ACLF (4, 26, 27). This excessive 'cytokine storm', even observed in ACLF patients without bacterial infection, may cause tissue damage, either by direct effects of inflammatory mediators on cell function but also as a consequence of organ hypoperfusion (10, 28, 29). This process when protracted evolves to immune exhaustion that can cause secondary infections and organ failure resembling the immunological response observed in patients with severe sepsis (10, 28, 29). In the current study, we observed that patients with ACLF did not develop more new infections or septic shock compared to medical ICU or sepsis cohorts during their ICU stay. Furthermore, in all 3 study groups white blood cell counts were similarly elevated throughout the first week in the ICU, suggesting a comparable immunological response. In addition, the acute cytokine response on day 1 in the ICU appeared largely

similar in ACLF patients and septic patients when matched for severity of illness and baseline risk factors. In our study we did observe lower CCL-13 and higher TNF- α levels in ACLF patients which were already observed by others (30). Circulating C-reactive protein was significantly lower in ACLF patients than in septic or other medical ICU patients, likely explained by a lower C-reactive protein secretion rate due to liver dysfunction, making it a less reliable marker to assess severity of inflammation in this specific population (31-33). However although CRP levels were lower in ACLF, they mirrored the CRP levels observed in the septic and medical ICU patients peaking at day 2-3 in all populations. Overall, the similar inflammatory/immunological response could, at least in part, explain why ACLF and critically ill non-ACLF patients displayed the same incidence of new infections and new septic shock in our study.

Taken together, our data suggest that patients with ACLF should have the same initial ICU management as other ICU populations. ACLF patients, when eligible, may additionally benefit from transplantation and should be evaluated timely if this therapy is deemed appropriate. This was already suggested by Gustot *et al.*, who observed that ACLF is a very dynamic clinical syndrome and that the evolution of the ACLF grade between diagnosis and day 4-7 was the best predictor of short-term mortality (5). Furthermore a recent study showed that liver transplantation even in the most severely ill ACLF grade 3 patients, improved their poor prognosis and had similar survival rates as transplanted patients with lower ACLF grades (34). Importantly, whereas ICU, hospital and 90-day mortality were comparable, liver-transplant-free 90-day mortality tended to be higher in patients with ACLF compared to non-ACLF septic patients in our study that confirms the fact that patients with cirrhosis remain at higher risk even after successful ICU care. Although our study may have been underpowered to detect more subtle differences in mortality, these findings should indeed further encourage physicians to evaluate ACLF patients for liver transplantation during their ICU stay and within 90 days after successful ICU admission (13, 35, 36). A difference in survival rate in transplanted versus non-transplanted ACLF patients was already observed during the first 50 days by other investigators although more work is

clearly needed to establish the effect of ICU admission *per se* on transplant outcomes in frail ICU survivors (34).

This study has several limitations. First, as indicated above, the study may have been underpowered to detect specific differences between ACLF and non-ACLF patients. Also, we only quantified plasma cytokine levels on day 1, a potential different response in ACLF patients to more prolonged critical illness can therefore not be excluded.

In conclusion, ACLF patients ~~with organ failure~~ admitted to the ICU display a similar initial inflammatory host response and a comparable short-term ICU outcome compared to matched septic or other medical ICU patients. Together, these findings suggest that ICU care in patients with cirrhosis and organ failure is not universally futile and warrants the same ICU treatment considered in non-cirrhotic patients with end organ failure. In addition ACLF patients should be evaluated for liver transplantation early on during their ICU stay.

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Table 1: ICU admission parameters of ACLF-patients compared to non-ACLF-patients.

	ACLF ICU patients N=71	septic ICU patients N=71	p-value “ACLF vs. septic”	medical ICU patients N=71	p-value “ACLF vs. medical ”
Male sex – no.	45 (63%)	45 (63%)	>0.9	52 (73%)	0.2
Age – yr	59 ± 1	61 ± 2	0.3	58 ± 2	0.6
BMI – kg/m ²	26.5 ± 0.6	26.3 ± 0.7	0.8	27.7 ± 0.8	0.3
Diabetes mellitus – no.	22 (31%)	26 (37%)	0.5	22 (31%)	>0.9
Malignancy – no.	13 (18%)	12 (17%)	0.8	16 (23%)	0.5
Pre-admission dialysis – no.	1 (1%)	1 (1%)	>0.9	1 (1%)	>0.9
NRS score > 4 – no. ^A	35 (49%)	34 (48%)	0.9	32 (45%)	0.6
Randomization to early PN – no.	39 (55%)	38 (54%)	0.9	40 (56%)	0.9
Infection upon admission – no.	53 (75%)	71 (100%)	<0.0001	53 (75%)	>0.9
Sepsis upon admission – no.	50 (70%)	71 (100%)	<0.0001	50 (70%)	>0.9
Diagnostic category at ICU admission			<0.0001		<0.0001
ACLF	71	0		0	
Other gastroent. or hepatic disease	0	0		20	
Cardiovascular disease	0	2		3	
Hematologic or oncologic disease	0	2		6	
Neurological disease ^B	0	2		5	
Renal disease	0	2		4	
Respiratory disease	0	15		30	
Complicated surgery ^C	0	21		0	
Cardiac surgery	0	9		0	
Trauma/burns	0	6		0	
Transplantation	0	4		0	
Other	0	8		3	
Day 1 plasma parameters					
Bilirubin - mg/dl	3.7 [1.7-10.6]	0.8 [0.5-1.4]	<0.0001	0.8 [0.5-1.5]	<0.0001
AST - IU/l	62 [41-141]	62 [24-148]	0.3	69 [25-156]	0.5
ALT - IU/l	31 [19-62]	34 [16-109]	0.9	39 [19-118]	0.4
ALP - IU/l	189 [130-267]	150 [115-239]	0.1	181 [130-273]	0.9
GGT - IU/l	49 [25-104]	42 [21-104]	0.5	55 [27-127]	0.4
Creatinine - mg/dl	1.6 [0.8-2.4]	1.1 [0.7-2.8]	0.4	1.6 [0.8-2.4]	0.3
Urea - mg/dl	94 ± 6	85 ± 9	0.4	101 ± 10	0.5
CRP - mg/l	66 ± 8	138 ± 13	<0.0001	157 ± 16	<0.0001
APACHE II score ^D	36 ± 1	35 ± 1	0.4	35 ± 1	0.5
Day 1 SOFA score ^E	12 ± 1	9 ± 1	<0.0001	9 ± 1	<0.0001
Day 1 CLIF-SOFA ^F	13 ± 1	-	-	-	-
Day 1 Mechanical ventilation – no.	55 (77%)	65 (91%)	0.02	56 (78%)	0.8
Day 1 Renal replacement therapy – no.	4 (5%)	6 (8%)	0.5	4 (5%)	0.9
Day 1 Pharmacological hemodynamic support – no.	51 (71%)	46 (64%)	0.4	35 (49%)	0.006

Data are presented as mean±SEM, median [IQR] or number of patients (%).^A Scores on nutritional risk screening (NRS) range from 0 to 7 with higher scores indicating a higher risk of malnutrition (Kondrup et al ClinNutr 2003). ^B Neurologic disease combines patients admitted to the ICU with a neurologic

disease or with a neurologic presentation of medical disease ^C Complicated surgery indicates patients suffering from complications after abdominal or pelvic surgery, pulmonary or esophageal surgery, neurosurgery or vascular surgery. ^D The Acute Physiology and Chronic Health Evaluation II (APACHE II) score reflects severity of illness with higher values indicating more severe illness ^E The Sequential Organ Failure Assessment Score (SOFA) calculated on the first day in ICU (37). ^F Chronic liver failure-SOFA score was post-hoc calculated for the ACLF patients on the first day in ICU.

Table 2: ICU outcome parameters of ACLF-patients compared to non-ACLF-patients

	ACLF ICU patients N=71	septic ICU patients N=71	p-value "ACLF vs. septic"	medical ICU patients N=71	p-value "ACLF vs. medical "
ICU stay – days	10 [4-16]	9 [3-17]	0.8	9 [5-18]	0.9
Hospital stay - days	27 [14-48]	25 [14-61]	0.6	24 [12-56]	0.9
Liver dysfunction					
Max. bilirubin in ICU – mg/dl	6.1 [3.1-19.6]	1.5 [0.6-3.1]	<0.0001	1.2 [0.7-3.4]	<0.0001
Max. AST in ICU – IU/l	125 [73-286]	92 [38-263]	0.04	99 [39-264]	0.1
Max. ALT in ICU – IU/l	55 [31-146]	71 [26-229]	0.9	66 [30-190]	0.7
Max. ALP in ICU – IU/l	366 [234-494]	339 [168-687]	0.8	341 [235-494]	0.9
Max. GGT in ICU – IU/l	85 [47-183]	114 [48-299]	0.1	112 [57-260]	0.1
Mechanical ventilation – no.	64 (90%)	66 (93%)	0.5	63 (89%)	0.8
Duration mechanical ventilation – days	7 [3-12]	6 [3-13]	0.5	8 [4-19]	0.09
Hemodynamic support – no. ^A	49 (70%)	54 (76%)	0.3	45 (63%)	0.5
Duration hemodynamic support - days	4 [2-9]	5 [3-12]	0.3	5 [3-13]	0.3
Kidney failure					
Renal replacement therapy – no.	21 (30%)	18 (25%)	0.6	26 (37%)	0.4
Duration RRT – days	8 [4-14]	10 [4-35]	0.2	7 [5-15]	0.8
Max. creatinine in ICU – mg/dl	1.7 [1.1-3.1]	1.3 [0.8-3.6]	0.3	2.5 [0.9-4.5]	0.2
Max. urea in ICU – mg/dl	146 ± 11	122 ± 10	0.1	149 ± 12	0.9
New infection – no.	30 (42%)	27 (38%)	0.6	32 (45%)	0.7
Max. CRP in ICU – mg/l	102 ± 9	223 ± 13	<0.0001	222 ± 16	<0.0001
Septic shock – no.	24 (34%)	18 (25%)	0.3	17 (24%)	0.2
Steroid treatment – no.	36 (51%)	40 (56%)	0.5	43 (61%)	0.2
ICU mortality – no.	17/71 (24%)	16/71 (23%)	0.7	16/71 (23%)	0.8
Hospital mortality – no.	24/71 (32%)	18/71 (25%)	0.3	22/71 (31%)	0.7
90-day mortality – no. ^B	28/70 (40%)	19/71 (27%)	0.1	21/68 (31%)	0.3
LT free ICU mortality – no.	16/64 (25%)	16/71 (23%)	0.8	16/71 (23%)	0.8
LT free hospital mortality – no.	22/62 (35%)	18/71 (25%)	0.2	22/71 (31%)	0.6
LT free 90-day mortality – no.	26/61 (43%)	19/71 (27%)	0.06	21/68 (31%)	0.2

^A hemodynamic support is the combination of pharmacological and mechanical hemodynamic support.

^B Data on vital status at 90 days was not available from 4 non-Belgian citizens (1 ACLF patient, 3 medical-non-ACLF patients). LT is liver transplant.

Table 3: A multivariate Cox proportional hazard analysis of the impact of presence of ACLF on time to alive discharge from ICU

Multivariate corrected for admission risk factors	Likelihood [hazard ratio (95% CI)] for earlier alive ICU discharge	p-value
1. Comparison 1 (ACLF and other septic ICU patients)		
Malignancy	1.92 (1.17-3.05)	0.01
Diabetes	1.13 (0.74-1.71)	0.5
APACHE II score (per unit added)	0.95 (0.93-0.98)	0.002
Sepsis on admission	0.56 (0.32-1.00)	0.05
Presence of ACLF	0.82 (0.53-1.25)	0.3
1. Comparison 2 (ACLF and other medical ICU patients)		
Malignancy	1.80 (1.08-2.89)	0.02
Diabetes	1.25 (0.82-1.89)	0.2
APACHE II score (per unit added)	0.94 (0.92-0.96)	<0.0001
Sepsis on admission	0.60 (0.40-0.91)	0.01
Presence of ACLF	0.96 (0.65-1.40)	0.8

Table 4: Serum cytokine concentration on day 1 in ICU of ICU patients with acute-on-chronic liver failure vs. matched septic ICU patients

median [IQR] pg/ml	ACLF ICU patients (n=50)	Non-ACLF patients with sepsis (n=50)	p-value
CCL13	30.2 [16.0-60.5]	36.6 [26.0-75.3]	0.03
CCL2	434.6 [207.3-792.1]	588.7 [248.3-1162.9]	0.4
CCL3	22.7 [15.7-42.4]	18.6 [11.5-33.0]	0.8
IFN γ	3.4 [1.7-11.6]	2.7 [0.7-15.9]	0.1
IL-10	1.7 [0.6-4.8]	1.8 [0.6-5.0]	0.8
IL-1 β	0.2 [0.1-0.3]	0.2 [0.1-0.5]	0.2
IL-6	34.4 [11.9-167.2]	34.2 [7.6-150.2]	0.7
IL-8	63.5 [37.5-157.6]	34.0 [15.3-76.6]	0.1
TNF	3.7 [2.5-7.2]	2.5 [1.8-5.0]	0.02

Figure1

Figure 1: CRP , white blood cell and platelet count during the first week in ICU. CRP (graph A and B) is presented as mean $\pm$ SEM, White blood (graph C and D) cell and platelet count (graph E and F) as median and interquartile ranges. * $p < 0.0001$. The left panel (graph A, C and E) represent patients diagnosed with ACLF (black line, white boxes, n=71) compared to matched “septic ICU patients”**

(dotted line, gray boxes, n=71). The right panels (graph B, D and F) represent patients diagnosed with ACLF (black line, white boxes, n=71) compared to matched “medical ICU patients” (dotted line, gray boxes, n=71).

Supplemental table 1: ICU admission parameters of ACLF and non-ACLF patients of which cytokine levels were quantified on day 1 in ICU.

	ACLF ICU patients N=50	septic ICU patients N=50	p-value “ACLF vs. septic”
Admission characteristics			
Male sex – no.	32 (64%)	34 (68%)	0.7
Age – yr	60 ± 1	61 ± 2	0.5
BMI – kg/m ²	26.6 ± 0.7	27.6 ± 0.9	0.4
Diabetes mellitus – no.	18 (36%)	20 (40%)	0.7
Malignancy – no.	7 (14%)	10 (20%)	0.4
Pre-admission dialysis – no.	1 (2%)	0 (0%)	0.3
NRS score > 4 – no.	24 (48%)	21 (42%)	0.5
Randomization to early PN – no.	28 (56%)	33 (66%)	0.3
APACHE II score	36 ± 1	36 ± 1	0.9
Infection upon admission – no.	34 (68%)	50 (100%)	<0.0001
Sepsis upon admission– no.	32 (64%)	50 (100%)	<0.0001
Diagnostic category at ICU admission			<0.0001
ACLF	50	0	
Other gastroent. or hepatic disease	0	13	
Cardiovascular disease	0	1	
Hematologic or oncologic disease	0	4	
Neurological disease	0	5	
Renal disease	0	3	
Respiratory disease	0	14	
Complicated surgery	0	7	
Other	0	3	
Day 1 plasma parameters			
Bilirubin - mg/dl	5.0 [2.6-14.0]	0.7 [0.4-1.3]	<0.0001
AST - IU/l	72 [40-150]	40 [20-78]	0.007
ALT - IU/l	31 [19-77]	30 [17-87]	0.4
ALP - IU/l	188 [141-259]	180 [117-309]	0.9
GGT - IU/l			0.6
Creatinine - mg/dl	42 [24-94]	48 [24-127]	0.8
Urea - mg/dl	2.0 ± 0.2	1.9 ± 0.2	0.01
CRP - mg/l	105 ± 7	79 ± 8	<0.0001
	56 ± 9	175 ± 20	