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EASL Clinical Practice Guidelines on acute-on-chronic liver failure☆

European Association for the Study of the Liver*

Summary

Acute-on-chronic liver failure (ACLF), which was described relatively recently (2013), is a severe form of acutely decompensated cirrhosis characterised by the existence of organ system failure(s) and a high risk of short-term mortality. ACLF is caused by an excessive systemic inflammatory response triggered by precipitants that are clinically apparent (*e.g.*, proven microbial infection with sepsis, severe alcohol-related hepatitis) or not. Since the description of ACLF, some important studies have suggested that patients with ACLF may benefit from liver transplantation and because of this, should be urgently stabilised for transplantation by receiving appropriate treatment of identified precipitants, and full general management, including support of organ systems in the intensive care unit (ICU). The objective of the present Clinical Practice Guidelines is to provide recommendations to help clinicians recognise ACLF, make triage decisions (ICU *vs.* no ICU), identify and manage acute precipitants, identify organ systems that require support or replacement, define potential criteria for futility of intensive care, and identify potential indications for liver transplantation. Based on an in-depth review of the relevant literature, we provide recommendations to navigate clinical dilemmas followed by supporting text. The recommendations are graded according to the Oxford Centre for Evidence-Based Medicine system and categorised as 'weak' or 'strong'. We aim to provide the best available evidence to aid the clinical decision-making process in the management of patients with ACLF.

Introduction

Acutely decompensated cirrhosis refers to the development of ascites, encephalopathy, gastrointestinal haemorrhage, or any combination of these disorders in patients with cirrhosis (Fig. 1). Acutely decompensated cirrhosis may occur at different points in the course of disease and generally leads to non-elective admission to the hospital.[1] Acute-on-chronic liver failure (ACLF) is a severe form of acutely decompensated cirrhosis; it is associated with a 28-day mortality rate of 20% or more (*vs.* 5% or less among patients with acutely decompensated cirrhosis without ACLF).[2] ACLF is characterised by the functional failure of one or more of the six major organ systems (*i.e.*, liver, kidney, brain, coagulation, circulation, and respiration; Fig. 2; Tables S1 and S2), and systemic inflammation, that may have been induced by acute precipitants (*i.e.*, intrahepatic or extrahepatic insults, or both).[2,3] This general definition, which is an evidence-based definition developed under the auspices of the European Association for the Study of the Liver (EASL)-Chronic Liver Failure (CLIF) Consortium (CLIF-C), is accepted and operational in a large number of countries across different continents.[4] Of note, the Chinese Group on the Study of Severe Hepatitis B (COSSH) proposed a definition for ACLF that develops among patients with hepatitis B virus (HBV)-related chronic liver disease, a definition which was very close to the European definition of ACLF (Tables S3).[5] However, there are other definitions of ACLF, for example the definition proposed by the Asia Pacific Association for the Study of the Liver (APASL[6]), or the definition proposed by the North American Consortium for the Study on End-Stage Liver Disease (NACSELD[7]). Each of these definitions differs from the EASL-CLIF-C definition on several points that have been recently reviewed elsewhere.[4,8,9] The definition of ACLF proposed by APASL is restricted to patients with acute liver dysfunction triggered by acute intrahepatic precipitants; applies to patients with cirrhosis and no prior decompensation episode, and also to those with non-cirrhotic chronic liver disease.[6] Consequently, they do not consider bacterial infection, gastrointestinal bleeding or surgery as potential precipitating events for the development of ACLF. The definition of ACLF proposed by the NACSELD is also based on expert opinion and only captures the most severe patients receiving organ support (Tables S4).[7] In their definition, they do not consider the severity of liver dysfunction or coagulopathy. Thus, in the present EASL Clinical Practice Guidelines (CPGs), the term ACLF will refer to the EASL-CLIF-C definition of ACLF, unless otherwise specified.

Keywords: Organ failure; inflammation; precipitating event; infection; alcohol-related hepatitis; critical care; organ support; sarcopenia; frailty; liver transplantation; prognosis; futility; mortality.
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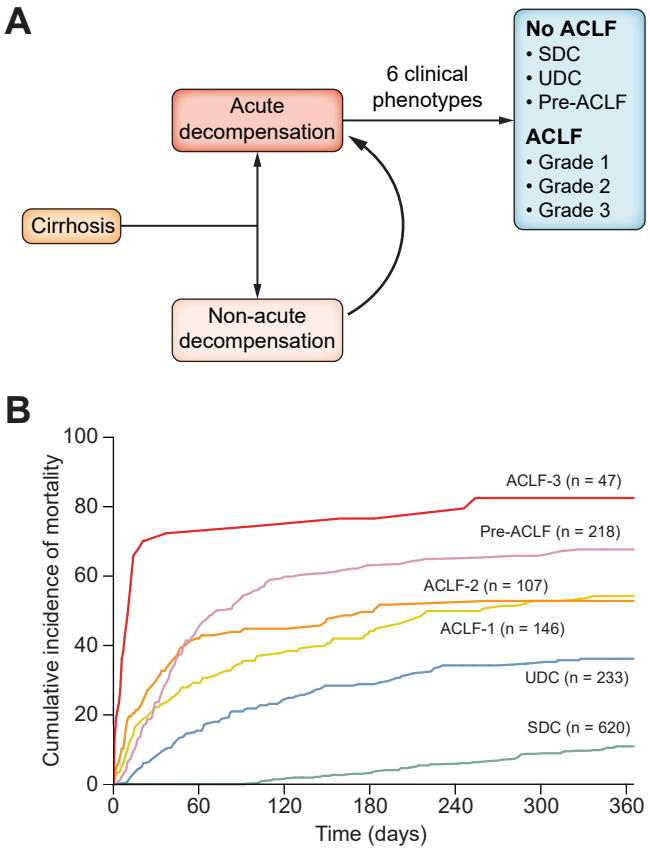


Fig. 1. Clinical trajectory of patients with cirrhosis. (A) Shows that patients can suffer either from acute decompensation, which implies need for hospitalisation with an acute liver-related complication or a less well-defined entity, called non-acute decompensation, which refers to the occurrence of a progressive liver-related complication that does not lead to hospitalisation. Patients with acutely decompensated cirrhosis without ACLF at presentation can be retrospectively classified into three distinct groups according to the three distinct disease trajectories during the 3 months after admission. Patients can be categorised as having SDC (patients in this group were discharged and not readmitted during the 3-month follow-up), UDC (patients in this group developed liver-related complications, but not ACLF, and were readmitted during the 3-month follow-up), or pre-ACLF (because patients in this group developed ACLF during the 3-month follow-up). Patients who present with ACLF meet criteria for one of three grades of ACLF. Overall, patients with acutely decompensated cirrhosis may therefore be divided into six distinct groups. Modified from Jalan *et al.*[194] and D'Amico *et al.*[1] (B) shows the outcomes of the six groups (Reproduced from[194]). ACLF, acute-on-chronic liver failure; SDC, stable decompensated cirrhosis; UDC, unstable decompensated cirrhosis.

Information on ACLF and its management have already been provided in the EASL CPGs on the management of decompensated cirrhosis published in 2018. Unless indispensable, this information will not be repeated in the present document, which refers to several important studies published since 2018 and addresses new questions relative to those addressed in the previous EASL CPGs.[10]

The objective of the present CPGs is to provide recommendations to help clinicians to recognise ACLF, make triage decisions (intensive care unit [ICU] *vs.* no ICU), identify and manage acute precipitants, identify organ systems that require support or replacement, define potential criteria for futility of intensive care, and identify potential indications for liver transplantation.

Methodology used to develop the present guidelines

The EASL Governing Board initiated these CPGs in October 2021 by selecting a panel of experts and describing the remit of the assignment. The development of these CPGs followed a standard operating procedure set out by EASL[11] and meets the international standards for CPGs set out by the Guidelines International Network. The process involves identification of several key questions pertinent to the subject matter. The CPG panel drafted questions according to the PICO format. P – patient, problem, or population, I – intervention, C – comparison, control or comparator, O – outcome. PICO questions were vetted through a simplified Delphi process by a 38-member panel, including clinicians, patients, and other stakeholders competent in the field of acutely decompensated cirrhosis beyond the CPG panel and the EASL Governing Board. Every PICO question that did not reach >80% agreement in the first round of the Delphi process was revised; the revised questions were then submitted for approval by the Delphi panelists in a second round. Once the final PICO questions had been determined, a systematic literature search was performed using PubMed, and expanding to Embase, Google Scholar and Scopus when needed. Each expert took responsibility, made proposals for statements and recommendations for a specific section of the guideline and shared tables of evidence and text with the full panel. The panel met virtually on 10 occasions, and all recommendations were discussed and approved by all participants. The level of evidence was graded according to the Oxford Centre for Evidence-Based Medicine system (Table 1)[12] and the strength of the recommendations was categorised as either 'weak' or 'strong' (Table 2). The higher the quality of the evidence, the more likely a strong recommendation was made. If no clear evidence was available, recommendations were based on the expert opinion of the panel members. All recommendations were subsequently submitted for approval through a third Delphi round. The classification of consensus strength was as follows: Strong consensus if >95% agreement, consensus if >75% to 95% agreement, majority agreement if >50 to 75% agreement, no consensus if <50% agreement. The technical solution has been supported by the Clinical Guideline Service group (https://www.guidelineservices.com), which has provided an online platform, where all CPG documents have been uploaded and reviewed. All recommendations were ultimately brought to the attention of the EASL Governing Board for final approval.

Defining ACLF

Should patients with previous episodes of decompensated cirrhosis be considered in the definition of ACLF?

Recommendations

- Both patients with prior decompensation and those without should be included in the definition of ACLF (**LoE 2, strong recommendation, strong consensus**).

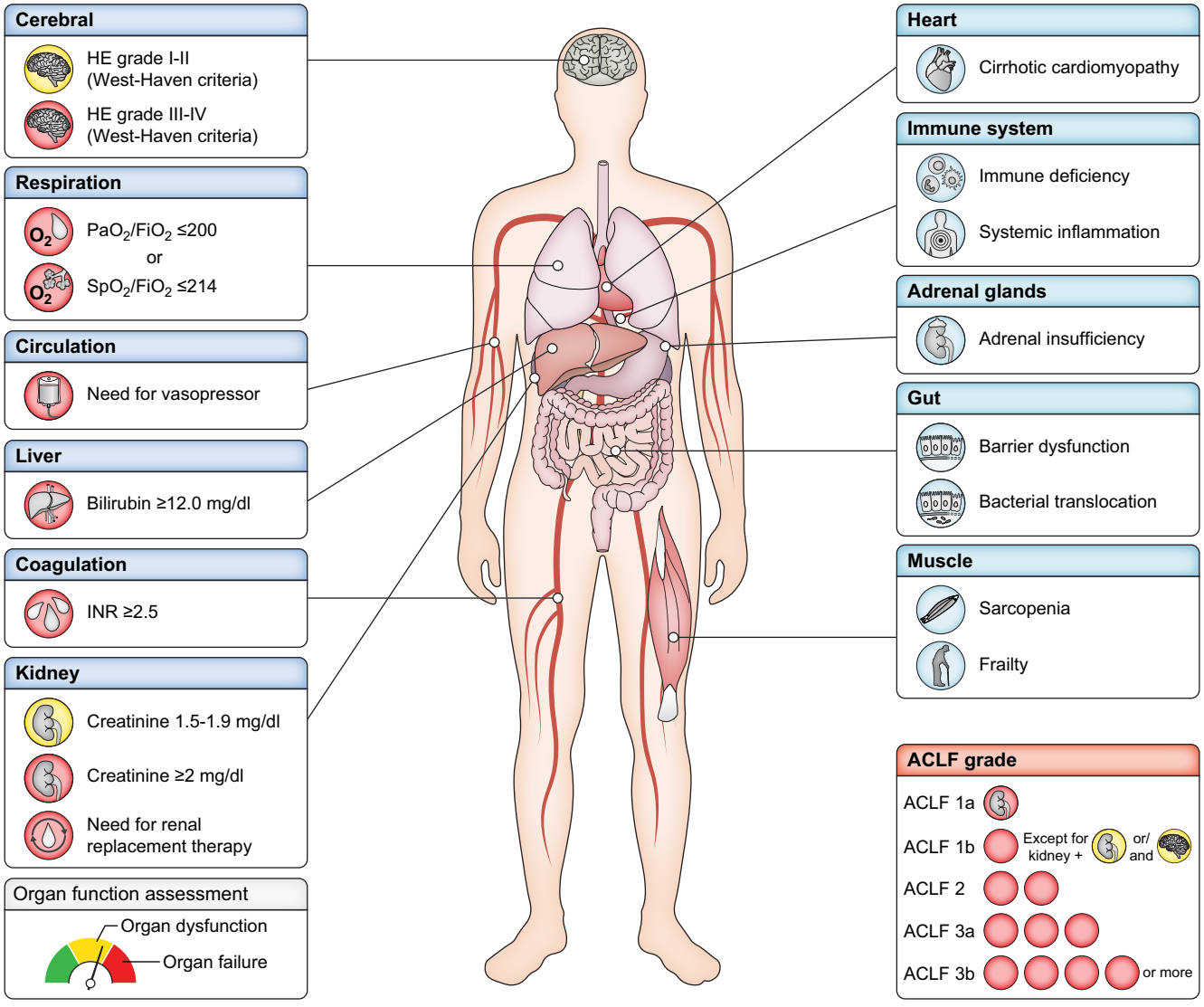


Fig. 2. Organ systems involved in ACLF.[2,4,15] On the left are shown each of the 6 organ systems explored by CLIF-C OF scoring system; the red color indicates the criteria for organ failure and the orange color indicates criteria for kidney or cerebral dysfunction. Box in the right bottom corner shows the criteria established by the EASL-CLIF Consortium to define the presence of ACLF and its grade. On the right, in light blue, are shown additional organ systems whose function is altered in patients with ACLF.

Table 1. Level of evidence based on the Oxford Centre for Evidence-based Medicine (adapted from The Oxford 2011 Levels of Evidence).

Level	Criteria	Simple model for high, intermediate and low evidence
1	Systematic reviews (SR) (with homogeneity) of randomised-controlled trials (RCT)	Further research is unlikely to change our confidence in the estimate of benefit and risk
2	Randomised-controlled trials (RCT) or observational studies with dramatic effects; systematic reviews (SR) of lower quality studies (*i.e.* non-randomised, retrospective)	
3	Non-randomised controlled cohort/follow-up study/control arm of randomised trial (systematic review is generally better than an individual study)	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate
4	Case-series, case-control, or historically controlled studies (systematic review is generally better than an individual study)	
5	Expert opinion (mechanism-based reasoning)	Any estimate of effect is uncertain

Table 2. Grades of recommendation.

Grade	Wording	Criteria
Strong	Shall, should, is recommended. Shall not, should not, is not recommended.	Evidence, consistency of studies, risk-benefit ratio, patient preferences, ethical obligations, feasibility
Weak or open	Can, may, is suggested. May not, is not suggested.	

The controversy about whether patients with cirrhosis who have experienced prior decompensation should be included in the definition of ACLF resulted from the APASL criteria specifically excluding such patients from their definition of ACLF.[13] The first, multicentre, prospective study to systematically address whether previous decompensation impacted on short-term outcomes was the CANONIC study.[2] This multicentre study included 1,343 consecutive patients with cirrhosis who were hospitalised with acute decompensation and analysed the data agnostically to define markers of poor outcome. 279 patients (27.8%) with no ACLF and 66 patients (23.2%) with ACLF had no previous decompensation (p = 0.12), suggesting that prior decompensation had no effect on the occurrence of ACLF. However, paradoxically, patients with no previous decompensation were significantly more likely to have more severe grades of ACLF (16.5%; 27.6% and 42.9% for grades 1, 2 and 3, respectively; p <0.01). Among patients with ACLF, a higher percentage of patients without prior decompensation than patients with prior decompensation presented with active alcohol consumption (37.5% *vs*. 17.1%), any precipitant (71.9% *vs*. 59.8%), liver failure (47.9% *vs*. 35.7%), cerebral failure (28.7% *vs.* 19.9%), coagulation failure (39.4% *vs.* 28.9%) or respiratory failure (23.4% *vs.* 9.4%).[2] Markers of systemic inflammation such as white cell count (p <0.001) and C-reactive protein (p <0.03) were higher in those with no prior decompensation. The 28-day mortality rate was also significantly higher (42.2% *vs.* 29.6%; p = 0.03) in patients without prior decompensation compared to those with prior decompensation.[2] It is important to note that for any given value of leukocyte count, the probability of death was significantly higher in patients without prior decompensation than in those with prior decompensation.[2]

From the treatment perspective, excluding patients with prior decompensation from the definition of ACLF would prevent clinicians from using prognostic models that enable early recognition of likely poor outcome in these patients; thus, they would be less likely to receive intensive care, to be transferred to specialist units for management, or to be included in clinical trials of novel therapeutics. Most importantly, if prior decompensation is eliminated from the definition of ACLF, these patients will not receive ACLF-specific prioritisation for liver transplantation, as is currently being piloted in some countries such as the UK.

Organ systems that should be considered

Is the CLIF-C organ failure (OF) scoring system better at identifying severe organ failures than the other scoring systems?

Recommendations

- Organ failures as included in the EASL-CLIF-C criteria should be used for the diagnosis of ACLF (**LoE 2, strong recommendation, consensus**).
- The failure of one or more of the six major organ systems according to the EASL-CLIF-C criteria should be used to define the severity of ACLF and the risk of 28-day mortality (**LoE 2, strong recommendation, strong consensus**).
- The risk of 28-day mortality in a patient with ACLF should be assessed sequentially to evaluate their response to intervention (**LoE 2, strong recommendation, consensus**).

Statements

- Failure of the liver, kidneys, brain, coagulation, circulation, and/or respiration, as defined by the CLIF-C OF scoring system, confers a high case fatality rate at 28 days in patients with acutely decompensated cirrhosis (**LoE 2, strong consensus**).
- The number of organ failures according to the CLIF-C OF score that are simultaneously present is associated with increasing case fatality rate at 28 days (**LoE 2, strong consensus**).
- The CLIF-C OF score, as part of the CLIF-C ACLF score and ACLF grade, has been validated for sequential use and can be used repeatedly to determine the risk of 28-day mortality (**LoE 2, strong consensus**).
- The CLIF-C OF score has been validated in many countries around the world (**LoE 2, strong consensus**).
- The NACSELD classification for the diagnosis of ACLF underestimates the risk of death of patients with acutely decompensated cirrhosis. Therefore, the NACSELD score underestimates the 28-day and 90-day mortality of patients with acutely decompensated cirrhosis (**LoE 2, strong consensus**).
- The AARC (APASL ACLF research consortium) score is applied to patients diagnosed as having ACLF using the APASL criteria. As the APASL criteria underestimate the risk of death of patients with ACLF diagnosed using the EASL-CLIF-C criteria, the AARC score also underestimates 28-day and 90-day mortality in these patients (**LoE 2, consensus**).

Investigators from Europe (CLIF-C) and China (COSSH) use the CLIF-C OF scoring system, which uses different clinical and biochemical characteristics to assess the function of the six major organ systems (liver, kidney, brain, coagulation, circulation, respiration; Fig. 2; Tables S1).[4,5,9,14,15] The presence of one organ system failure or more, with a maximum of six is the cornerstone of the European and Chinese definitions of ACLF (Tables S2 and S3, respectively).[4,5,9,14,15] The North American investigators (NACSELD) only consider the function of four organ systems (brain, kidneys, circulation, respiration)[7] (Tables S4). Curiously, liver and coagulation are not considered, and kidney, circulatory and respiratory failures are defined by the physicians' response to the problem, namely the need for renal replacement therapy, inotropes, or mechanical ventilation, respectively. The NACSELD score is determined by the number of organ system failures (and therefore ranges from 1 to 4); ACLF is defined by a NACSELD score of 2 or more, with maximum of 4 (Tables S4).[16]

Investigators from APASL have developed the AARC score that explores the perturbation of brain function, the blood levels of bilirubin, prothrombin time or international normalised ratio (INR), creatinine, and lactate (Tables S5).[6] Of note, unlike the CLIF-C OF and NACSELD scores, the AARC score is not used to define ACLF but only to assess the severity of ACLF (as defined by APASL). In other words, the AARC score is applied to patients that are identified as having ACLF using the APASL criteria. As per APASL, ACLF is only defined by an acute onset of liver failure in response to an acute hepatic insult characterised by jaundice, ascites and/or hepatic encephalopathy.[6] The diagnosis of ACLF is therefore made using different criteria. Hence, there are potentially four definitions and sets of prognostic criteria that constitute ACLF.[5]

The CANONIC study was the first to assess the importance of organ failures in defining the risk of 28-day mortality. The data summarised in Table 3 shows the association of individual organ system failures with 28-day case fatality rate. Table 3 also shows that the case fatality rate increases with the number of failing organ systems.[2] Of note, similar findings have been reported by Chinese investigators who applied the CLIF-C OF score to patients with HBV-related ACLF.[14] Given the fact that liver and coagulation failures are independently associated with high mortality rates and are not included in the North American approach (NACSELD criteria[7]), this approach may underestimate the number of patients at risk of short-term mortality. The Asian Pacific criteria do not attribute importance to organ failures and exclude patients with previous decompensation and those with extrahepatic insults, thereby excluding a substantial number of patients at high risk of short-term mortality.

The CLIF-C OF score has been validated across the world in all aetiologies for which it has been tested.[4]

Comparison of APASL, NASCELD and EASL diagnostic criteria

Comparison of CLIF-C of score- vs. NACSELD criteria-based ACLF diagnosis

In a retrospective US Veterans Affairs study of 19,082 patients with a CLIF-C OF score-based ACLF diagnosis, 11,955 (62.7%) patients, with 28-day and 90-day mortality rates of 21.1% and 35.3%, respectively, did not meet NACSELD criteria for ACLF.[17] In another study, an analysis of United Network for Organ Sharing database revealed that only 15.3% (1,561/10,198) of patients with a CLIF-C OF score-based ACLF diagnosis met the criteria for having NACSELD-ACLF, and importantly, 29.9% of patients with an ACLF-3 diagnosis using the CLIF-C OF score would not be diagnosed as having ACLF by the NACSELD criteria.[18] In a Chinese study of patients with cirrhosis secondary to HBV infection, patients who did not have a diagnosis of NACSELD-ACLF but who met criteria for a CLIF-C OF score-based ACLF diagnosis had 28-day and 90-day transplant-free survival of 59.1% and 40.6%, respectively.[19] Taken together, these data suggest that the NACSELD-ACLF diagnostic criteria underestimates the presence of ACLF and the risk of death of patients with acutely decompensated cirrhosis.

Comparison of CLIF-C of score- vs. APASL criteria-based ACLF diagnosis. Using the Veterans Affair administrative dataset, 76.0% (4,296/5,653) patients with a CLIF-C OF score-based ACLF diagnosis did not meet the criteria for APASL-ACLF despite having 28- and 90-day mortality rates of 37.6% and 50.4%, respectively.[20] This suggests that the APASL criteria fails to identify patients who have a high short-term mortality. In another Korean study of 340 patients who met the criteria for APASL and/or CLIF-C OF score-based ACLF diagnosis, 58.8% (200/340) met only the criteria for CLIF-C OF score-based ACLF diagnosis whilst 19.4% (66/340) met only the criteria for APASL-ACLF, suggesting that the APASL-ACLF criteria would have excluded a significant proportion of patients with 28- and 90-day mortality rates of 32.0% and 48.4%, respectively.[21] These data suggest that the APASL-ACLF diagnostic criteria underestimates the presence of ACLF and the risk of

Table 3. Case fatality rate at 28 days among patients of the CANONIC cohort, according to the number and type of organ failures and the presence or absence of kidney or brain dysfunction*

Number and type of organ failure	All patients	No kidney or brain dysfunction	Either kidney or brain dysfunction
	No. of deceased patients/total no. of patients (%)		
No organ failure	39/874 (4.5)	20/562 (3.6)	19/312 (6.2)
One organ failure	39/267 (14.6)	17/184 (9.2)	22/83 (26.5)
Liver failure	14/101 (13.9)	4/68 (5.9)	10/33 (30.3)
Cerebral failure	3/30 (10.0)	2/25 (8.0)	1/5 (20.0)
Coagulation failure	3/28 (10.7)	1/19 (5.3)	2/9 (22.2)
Circulation or lung failure	3/22 (13.6)	1/15 (6.7)	2/7 (28.6)
Kidney failure	16/86 (18.6)	9/57 (15.8)	7/29 (24.1)
Two organ failures	31/97 (32.0)	19/66 (28.8)	12/31 (38.7)
Three organ failures or more	33/42 (78.6)	25/29 (86.2)	8/13 (61.5)

*Adapted from ref. 2. Kidney dysfunction is defined by creatinine levels ranging from 1.5 mg/dl to 1.9 mg/dl and brain dysfunction by hepatic encephalopathy grade 1 or 2.

28-day mortality of patients with acutely decompensated cirrhosis.

Precipitants that should be considered

How should precipitant(s) of ACLF be identified?

Recommendations

- Every patient who is admitted for ACLF, or who develops ACLF during hospital stay, should undergo a systematic workup (summarised in Fig. 3) that seeks to identify the commonest precipitants, which include proven bacterial infection, alcohol-related hepatitis, gastrointestinal haemorrhage with haemodynamic instability, flare of HBV infection, hepatitis E virus infection, recent use of a drug known to cause cerebral failure, and recent use of a drug known to cause kidney failure **(LoE 2, strong recommendation, strong consensus).**
- Patients in whom the systematic workup fails to identify the presence of precipitant(s), among those that are expected, should undergo a case-by-case assessment, depending on the clinical context and based on a comprehensive list of all potential uncommon precipitants (Table 4) **(LoE 5, strong recommendation, strong consensus).**

Statements

- A precipitant of ACLF is an acute intrahepatic or extrahepatic insult that may cause organ dysfunction (**LoE 2, strong consensus**).
- The number of precipitants that are simultaneously present is a major determinant of the short-term outcome of patients with ACLF (**LoE 2, strong consensus**).

A precipitant is an acute intrahepatic or extrahepatic disorder that may cause an impairment in end-organ function (*i.e.*, ACLF) through direct or indirect mechanism(s). The PREDICT study, the only prospective study designed to identify the precipitants of ACLF,[3] revealed that four disorders should be considered as precipitants of ACLF, including proven bacterial infections, severe alcohol-related hepatitis, gastrointestinal haemorrhage with shock, hepatitis E virus infection, and acute encephalopathy caused by drugs. Of note, these precipitants were identified in Western countries. In China, the main precipitants of ACLF are flares of HBV infection and bacterial infections.[14] Diagnostic criteria for all these common precipitants, including flares of HBV infection are provided in Table 4.

Another important finding of the PREDICT study was the imbalance in the prevalence of precipitants of ACLF (Fig. 4). The two commonest single precipitants were severe proven bacterial infection and alcohol-related hepatitis. Gastrointestinal haemorrhage with shock was considered as a single precipitant in only 6 (2%) patients of a total of 273 patients with identified precipitants. In cirrhosis, drugs can cause acute encephalopathy (as defined in[22]); however, drug-induced acute encephalopathy was never seen as a single precipitant but was combined with one or more other precipitants. The most prevalent combination of precipitants was the simultaneous occurrence of severe alcohol-related hepatitis and proven bacterial infection. The number of precipitants identified with the use of systematic workup has major prognostic value; patients with two or more precipitants have a higher risk of death at 90 days than patients with only one precipitant or those with no identifiable precipitant.[3] Taken together, these findings indicate that the systematic workup shown in Fig. 3 should be used in every patient with ACLF to identify the commonest precipitants and their potential combination(s) where present. In addition, the panellists included hepatitis E virus infection, flares of HBV infection and drug-induced acute kidney injury (AKI), which was considered to be underestimated in the PREDICT study, among the disorders that should be systematically sought (Fig. 3). Several drugs including proton-pump inhibitors,[23] antibiotics (piperacillin/tazobactam, meropenem, ciprofloxacin, norfloxacin, metronidazole) and antifungals (fluconazole)[24] are known to cause acute encephalopathy in cirrhosis (as defined in[22]) at standard recommended dosages because of increased serum concentrations, which are caused by decreased renal clearance, increased volume distribution, or increased passage through the blood-brain barrier. Sedatives (opioids, benzodiazepines) should be considered as precipitants of acute encephalopathy. A comprehensive list of drugs that may cause AKI is provided in Tables S6.

The systematic workup shown in Fig. 3 fails to identify the existence of a precipitant in 35% of patients with ACLF.[3] Analysis of the literature, and the experience from clinical practice, led us to identify rare disorders that may precipitate ACLF and enrich the list of precipitants in Table 4. Diagnostic criteria of these rare precipitants are also provided in Table 4. In clinical practice, the identification of any of these rare precipitants is dictated by the clinical context, in particular the landscape of failing organs, and the knowledge of the frequency of precipitants. We are not aware of any ongoing study evaluating whether the number of indeterminate precipitants would be trimmed with the use of the comprehensive list of potential precipitants shown in Table 4.

Predicting ACLF and death

Is the CLIF-C acute decompensation (AD) score more accurate than other prognostic scores in predicting risk of development of liver-related complications, ACLF and 90-day transplantation-free mortality in patients without ACLF?

Recommendations

- In the patients without ACLF, the CLIF-C AD score should be used sequentially to provide prognostic information regarding 90-day, 180-day and 365-day mortality **(LoE 2, strong recommendation, strong consensus).**
- CLIF-C AD score, model for end-stage liver disease (MELD) score or MELD-Na score can be used to define risk of development of ACLF **(LoE 2, strong recommendation, consensus).**

Statements

- In patients with acutely decompensated cirrhosis and no ACLF, the CLIF-C AD score provides more accurate prognostic information than the MELD score, MELD-Na score, and the Child-Pugh score in predicting the risk of 90-day, 180-day and 365-day mortality **(LoE 2, consensus).**
- CLIF-C AD score, MELD score and MELD-Na score have similar ability to predict the occurrence of ACLF and all perform better than the Child-Pugh score **(LoE 2, consensus).**

Among patients admitted for acutely decompensated cirrhosis without ACLF (according to the EASL-CLIF-C criteria), the mortality rate at day 28 after presentation is only ~5% but it increases to 12.6% at 3 months, 18.3% at 6 months, and 27.6% at 1 year.[2,3,25] These data suggest that some patients with no ACLF are also at high risk of short-term mortality. They should be recognised early and treated as potentially high-risk patients requiring closer monitoring and interventions to prevent progression to ACLF and death. On the other hand, patients with acutely decompensated cirrhosis who are at low risk of mortality may be discharged early, potentially saving resources and distress for the patients and their relatives.

The CLIF-C AD score was derived from analysis of clinical data from the patients included in the CANONIC study who did not have ACLF at presentation.[2,25] Age, serum sodium, white cell count, creatinine, and INR were selected as the best predictors of mortality, and they were combined into a score ranging from 0-100. An increasing score is associated with an increased risk of death. The performance of the CLIF-C AD score at predicting 3-month mortality improved from days 2, 3-

Table 4. Potential precipitants of ACLF at presentation and diagnosis.

Precipitant	Diagnosis
Common precipitants[a,b]	
Proven bacterial infection	
Spontaneous bacterial peritonitis	Neutrophils in ascites ≥250/mm^3
Spontaneous bacterial empyema	Hydrothorax and no evidence of pneumonia on chest imaging and neutrophils in pleural fluid >500/mm^3 plus negative pleural fluid culture or positive pleural fluid culture and neutrophils in pleural fluid ≥250 cells/mm^3
Spontaneous/secondary bacteraemia	Spontaneous bacteraemia: positive blood cultures and no cause of bacteraemia; secondary bacteraemia: (1) catheter-related infection (positive blood and catheter's tip cultures); (2) bacteraemia occurring within 24 hours after an invasive procedure
Urinary tract infection	Abnormal urinary sediment (>10 leukocytes/field) and positive urinary culture or uncountable leukocytes per field if negative cultures
Pneumonia	Clinical features of infection and new infiltrates on chest imaging
Bronchitis	Clinical features of infection, no infiltrate on chest imaging and positive sputum culture
Skin and soft tissue infection	Clinical features of infection associated with swelling, erythema, heat, and tenderness in the skin
Cholangitis	Cholestasis, right upper quadrant pain and/or jaundice and radiological data of biliary obstruction
Secondary peritonitis	Neutrophils in ascites ≥250/mm^3 frequently ≥10,000/mm^3), and at least two of the following: low glucose levels (<50 mg/dl [2.8 mmol/L]), protein concentration >10 g/L and LDH levels >normal serum concentration (Runyon's criteria). High amylase and bilirubin levels in ascites and Gram's stain showing polymicrobial infection in the presence of gut perforation. Evidence of an intra-abdominal source of infection (abdominal computed tomography or surgery)
Clostridioides difficile infection	3 unformed stools or more, toxigenic *Clostridiodes difficile* in stool
Fungal infection	
Invasive candidiasis	Isolation of *Candida* species in one blood culture or more (candidemia) or from normally sterile body fluids (*e.g.* ascites, pleural fluid)
Probable invasive aspergillosis	Detection of *Aspergillus* by direct examination and/or culture of respiratory samples in the presence of radiological imaging compatible with lung infection
Alcohol-related hepatitis	Active alcohol consumption and - If liver biopsy is unavailable, use NIAA criteria, *i.e.*, presence of 3 of the following criteria: 1. Serum bilirubin > 3 mg/dl [>50 μmol/L] 2. AST >50 IU/ml 3. AST/ALT ratio >1.5 4. AST and ALT < 400 IU/ml - Liver biopsy: Macrovesicular steatosis with ≥1 of the following: neutrophil infiltration, hepatocyte injury (ballooning), and Mallory-Denk bodies. The presence of megamitochondria, satellitosis (neutrophils surrounding dying/dead hepatocytes), and cholestasis (bilirubinostasis) is common, and may relate to prognosis.
Gastrointestinal hemorrhage with shock	Hematemesis, melena, low haemoglobin levels, sudden decrease in haemoglobin levels (≥2 g/dl), or any combination of these disorders, and hypovolemic shock; endoscopy
Drug-induced brain injury	Medical history of recent administration of sedative, mainly benzodiazepines, or opioids compounds
Drug-induced acute kidney injury	Medical history of administration of nephrotoxic drugs or compounds: NSAIDs, renin-angiotensin-aldosterone antagonists, α1-adrenoceptor antagonists, IV contrast media or nephrotoxic antibiotics (*i.e.*, vancomycin, aminoglycosides) (a comprehensive list of drugs is provided in Tables S1)
Rare precipitants	
Extrahepatic	
Viral infection	
Epstein-Barr virus (EBV)	AST and ALT >x3 ULN IU/ml Viral Capsid Antigen (VCA)-IgM antibody, Early Antigen (EA-D) antibody, Epstein-Barr Nuclear Antigen (EBNA) antibody, EBV quantitative PCR
Cytomegalovirus (CMV)	AST and ALT >3x ULN IU/ml CMV IgG antibody CMV quantitative PCR
Herpes simplex virus (HSV 1, 2, 6)	AST and ALT >1,000 IU/ml, HSV 1 and 2 IgM antibodies, HSV qualitative PCR
Varicella zoster virus (VZV)	AST and ALT >1,000 IU/ml, VZV IgM antibodies, qualitative PCR

(*continued on next page*)

Table 4. (*continued*)

Precipitant	Diagnosis
Human immunodeficiency virus (HIV)	Mild elevations of AST and/or ALT, HIV-1/-2 antibodies, quantitative PCR
Parvovirus B19	AST and ALT >3-5 ULN IU/ml, parvovirus B19 IgM, qualitative PCR
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	Mild elevations of AST and/or ALT, positive PCR or rapid antigenic tests in respiratory samples
Influenza A, influenza B, syncytial respiratory virus	Mild elevations of AST and/or ALT, positive PCR in respiratory samples
Parasitic infection	
Visceral Leishmaniasis	Elevations of AST, ALT, AP and GGT, detection of Leishmania, parasite or DNA, in tissues of relevance (bone marrow aspirate> lymph nodes >liver biopsy; stain, PCR or culture) and serology (positive IgG and IgM antibodies)
Surgical or radiological intervention	Recent surgery or invasive radiological intervention (7-day time frame)
Intrahepatic	
Viral infection	
Hepatitis B virus (HBV) infection or reactivation	Elevated AST and ALT, elevated HBV DNA, elevated HBsAg (negative in S-variants), 10-25% positive anti-HBc IgM
Superimposed hepatitis D in patients with chronic HBV	AST and ALT >400 IU/ml, positive HDV IgM and IgG, elevated PCR (HDV RNA)
Superimposed hepatitis A	AST or ALT >400 IU/ml, serum bilirubin > 3 mg/dl (>50 μmol/L) and positive anti-HAV-IgM
Superimposed hepatitis E	AST and ALT >400 IU/ml, serum bilirubin > 3 mg/dl, anti-HEV-IgM (and IgG) and quantitative PCR (HEV RNA)
Superimposed hepatitis C	AST or ALT >400 IU/ml, serum bilirubin >3 mg/dl (>50 μmol/L) and elevated HCV RNA
Drug-induced liver injury (DILI)	Medical history of administration of hepatotoxic compounds, (drugs, over-the-counter medicine (OTCM) or herbals; check in LiverTox® ALT ≥5x ULN, ALT ≥3x ULN, ALP ≥2x ULN, plus bilirubin >2x ULN. Pattern of liver injury is classified according to R (ALT x ULN/ALP x ULN): hepatocellular: R≥5, cholestatic: R≤2 or mixed: 2>R<5. Liver biopsy is only required in sporadic cases
Wilson's disease	First manifestation of the disease or consequence of an abrupt discontinuation of the chelation therapy or of a superimposed viral hepatitis Leipzig criteria (Leipzig Scoring System[c]), high serum bilirubin levels (≥10 mg/dl, mainly indirect form), Coombs-negative haemolysis, mild-to-moderate rise of liver enzymes (<500 IU/ml), AST to ALT ratio >2.2, low serum ALP, ALP to total bilirubin ratio <4, severe coagulopathy, mild-moderate encephalopathy and altered copper metabolism indicated by low serum ceruloplasmin levels (<20 mg/dl) and high 24-hour cooper urinary excretion (>100 μg; usually > 500 μg/24h)
Flare of autoimmune hepatitis (AIH)	Medical history of non-adherence to immunosuppressive therapy, de-escalation of immunosuppressive therapy or postpartum period. Elevated levels of AST, ALT, hypergammaglobulinemia and increased IgG; positive (≥1/80) ANA, anti-SMA, anti-SLA/LP in type 1 AIH; anti-LKM 1 and 3, anti-LC-1 in type 2 AIH. Histological examination of liver biopsy specimens is not mandatory in case of previously established diagnosis but can aid differential diagnosis in case of response to a second exogenous insult (*e.g.*, viral or drug related hepatitis) on top of typical AIH. Hyperacute exacerbation of undiagnosed or misdiagnosed AIH can be possible. Liver biopsy is mandatory for the diagnosis and also in the assessment of seronegative cases with no hypergammaglobulinemia and normal IgG. Histological features may differ from "typical characteristics of AIH"[d] and seronegativity is highly possible early in acute AIH. Simplified AIH score is unreliable in AIH with liver failure.
Ischaemic hepatitis	High peak of AST and ALT (usually >1,000 IU/ml), serum bilirubin usually <3 mg/dl and deep coagulopathy (marked increase in INR that improves rapidly) Abdominal ultrasonography must confirm vascular patency. Echocardiography with evaluation of right and left ventricular function

ALP, alkaline phosphatase; ALT alanine aminotransferase; ANA, antinuclear antibodies; AST, aspartate aminotransferase; HBc, hepatitis B core; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HEV, hepatitis E virus; INR, international normalised ratio; LC, liver cytosol; LDH, lactate dehydrogenase; LKM, liver-kidney microsomal; NIAAA, National Institute on Alcohol Abuse and Alcoholism; NSAIDs, non-steroidal anti-inflammatory drugs; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SLA/SLP, soluble liver antigen/liver-pancreas; SMA, smooth muscle antigen; ULN, upper limit of normal.

[a]From references # [3] and #[195].

[b]There may be two simultaneous precipitants or more.

[c]The Leipzig Scoring System components include: 1. Kayser-Fleischer rings, 2. Neurologic symptoms or typical abnormalities at brain magnetic resonance imaging, 3. Serum ceruloplasmin, 4. Coombs-negative haemolytic anaemia, 5. Liver copper (in the absence of cholestasis), 6. Urinary copper (in the absence of acute hepatitis), 7. Molecular analysis of the *ATP7B* gene. The Leipzig scoring system is used for the diagnosis if it is previously undiagnosed; Wilson's disease is indicated by a total score of 4 or more.

[d]Possible histological features include centrilobular haemorrhagic necrosis, massive or submassive hepatic necrosis, central perivenulitis, portal lymphoid aggregates, plasma cell infiltration.

7, and 8-15 (C indices were 0.72, 0.75, and 0.77, respectively).[25] In an internal validation cohort of 500 patients, the CLIF-C AD score performed better than the MELD, MELD-Na and Child-Pugh scores in predicting 90-day, 180-day and 365-day mortality. In an external validation cohort of 225 patients, similar results were obtained but the CLIF-C AD score did not perform statistically significantly better than the MELD-Na score.[25] The risk of progression of acutely decompensated cirrhosis to ACLF was specifically studied in the PREDICT study. The data showed that the CLIF-C AD score performed

similarly to the MELD and MELD-Na scores but better than the Child-Pugh score (C indices were 0.7, 0.7, 0.7 and 0.64, respectively) (Fig. 5).[26]

Many subsequent studies have validated the CLIF-C AD score as a predictor of future ACLF and mortality independently in patients with acutely decompensated cirrhosis in Europe, China, and Brazil.[27–33] Furthermore, the prognostic utility of the score for ACLF development following insertion of a transjugular intrahepatic shunt[34,35] or elective surgery[36] has been validated.

Is the CLIF-C ACLF score more accurate than other prognostic models for patients with ACLF?

Recommendations

- In patients with ACLF, the CLIF-C ACLF score should be used sequentially to provide prognostic information (**LoE 2, strong recommendation, strong consensus).**

Statement

- In patients with ACLF, the CLIF-C ACLF score provides more accurate information than the MELD score, MELD-Na score, and Child-Pugh score in predicting the risk of 28-day and 90-day mortality (**LoE 2, strong consensus**).

In patients with ACLF, the ACLF grades (based on the number of organ failures) enable categorisation of patients with a wide range of 28-day and 3-month mortality risks. In order to develop a prognostic score specifically for patients with ACLF, the CLIF-C ACLF score was developed using data from the CANONIC study;[2] it combines the CLIF-C OF score together with age and white cell count into a score ranging from 0-100 (see also footnote of Table S1).[15] The C indices of the CLIF-C ACLF score for 28-day and 90-day mortality (0.76 and 0.73, respectively) were significantly better than those of the MELD score (0.69 and 0.66, respectively; p <0.001 each), MELD-Na score (0.68, 0.66; p <0.001 each) and Child-Pugh score (0.67 and 0.66, respectively; p <0.001) (Fig. 6). Similar results were obtained in the validation cohort.[15] As discussed in the section on the CLIF-C OF score, the APASL criteria fails to identify a significant proportion of patients with ACLF and hence the AARC score, which has been developed for patients with ACLF diagnosed using the APASL criteria would behave in a similar manner. More recently, a large multicenter study was described from India showing better performance of AARC and NACSELD criteria compared to the CLIF-C ACLF score, but the study excludes a considerable number of patients with ACLF who would be diagnosed using the EASL-CLIF-C criteria. The COSSH criteria have been specifically developed for patients with HBV-related ACLF (Tables S7) and therefore cannot be strictly compared with the CLIF-C ACLF score.

Following the publication of the CLIF-C ACLF score, it has been validated across the world in both single and multicentre studies[27–29,31,33,37–51] with largely similar results to those observed in the primary study. Studies performed in patients with ACLF admitted to the ICU showed that the CLIF-C ACLF score and general ICU scores had similar accuracy in predicting short-term death.[52,53] In an independent cohort, criteria defining CLIF-C ACLF score cut-offs for futility of ongoing intensive care were proposed and should be further validated.[54]

Several studies from the US and China have proposed new models and nomograms for prognostication of patients with ACLF that have shown some improvements on the CLIF-C ACLF score, though further validation is required.[55–58] Finally, a new approach to model factors associated with prognosis using unselected patient data from the time of admission was

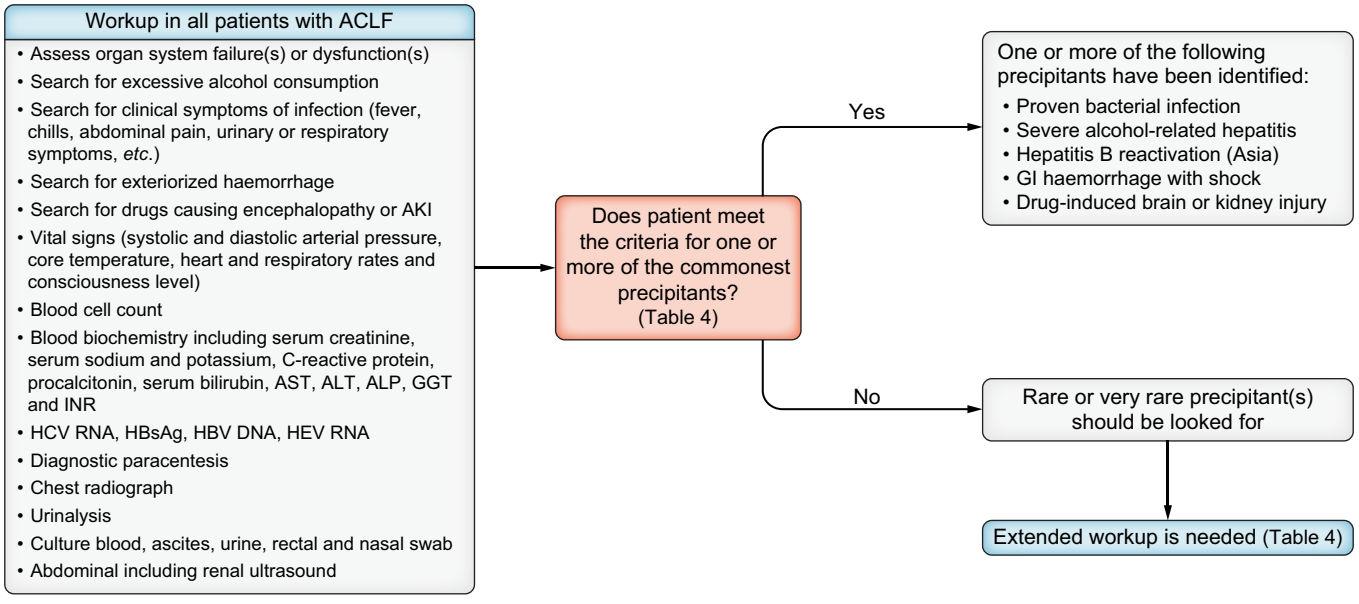


Fig. 3. Strategy for identification of precipitants in patients with ACLF. ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; INR, international normalised ratio.

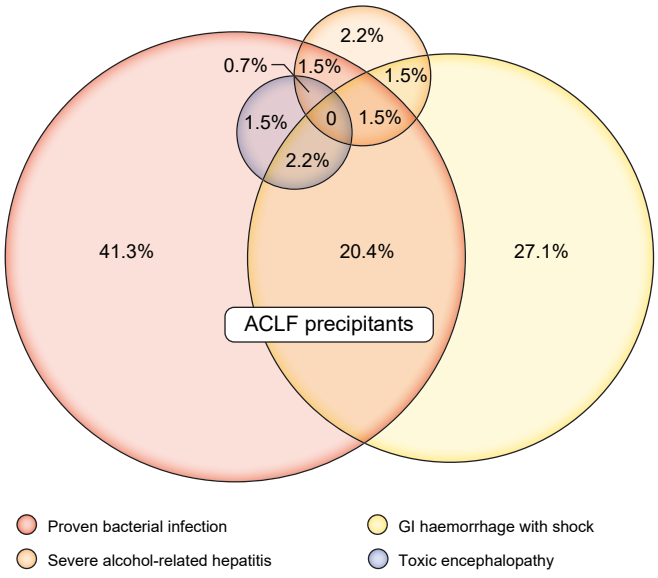
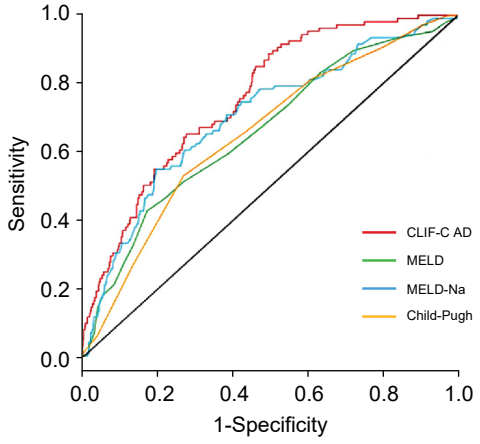


Fig. 4. Precipitants and their combination as identified in patients with ACLF enrolled in the PREDICT study.[3] Of the 420 patients with ACLF who have been studied in the PREDICT study, 273 had at least one clinically apparent precipitant and 147 had no clinically apparent precipitant. The Venn diagram shows the percentage of patients with a single precipitant and the percentage of patients for each combination of precipitants, each percentage being calculated with a denominator equal to 273 patients. ACLF, acute-on-chronic liver failure; GI, gastrointestinal.

shown to have high predictive ability in a population that predominantly had HBV; this score should be further validated in other populations.[59]



	AUROC (95% CI)	*p* value *vs.* CLIF-C ADs
CLIF-C AD	0.76 (0.71-0.80)	
MELD	0.66 (0.60-0.72)	0.0007
MELD-Na	0.70 (0.65-0.76)	0.0245
Child-Pugh	0.65 (0.60-0.71)	0.0004

Fig. 5. Predictive ability of CLIF-C AD score for 90-day mortality as compared to MELD, MELD-Na and Child-Pugh score. ACLF, acute-on-chronic liver failure; AD, acute decompensation; CLIF-C, EASL-chronic liver failure consortium; MELD, model for end-stage liver disease. (Reproduced from[25]).

Fig. 7 shows a model for the clinical use of the CLIF-C OF, CLIF-C AD, and CLIF-C ACLF scores that has been proposed by European investigators.[60]

Management

ICU admission

Would the application of the proposed criteria (Box 1) be helpful to select patients for admission to the ICU?

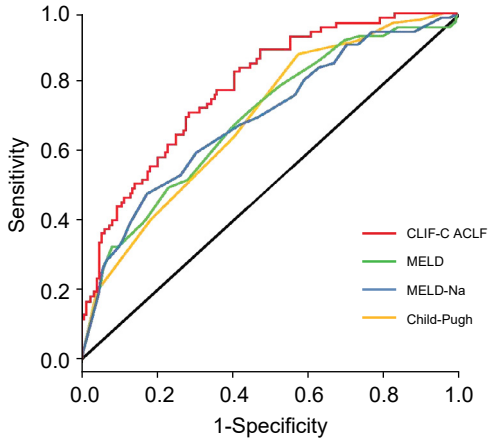
Recommendations

- Patients with ACLF requiring close monitoring or organ support should be admitted to the ICU **(LoE 3, strong recommendation, strong consensus).**
- Admission of patients with ACLF and severe comorbidities to the ICU is suggested to be considered on a case-by-case basis **(LoE 5, weak recommendation, consensus).**
- Prognosis in patients with ACLF should be determined after 3-7 days of full organ support **(LoE 4, strong recommendation, strong consensus).**
- The presence of ≥4 organ failures or a CLIF-C ACLF score >70 points in individuals with no option for salvage liver transplantation are criteria to consider withdrawal of organ support and palliative care after 3-7 days of full organ support **(LoE 4, strong recommendation, strong consensus).**

Statement

- Criteria for deciding admission to the ICU for patients with ACLF are similar to those applied in the population of patients without cirrhosis since outcomes are similar when baseline clinical characteristics are similar **(LoE 4, consensus).**

Patients with acutely decompensated cirrhosis are prone to develop organ failure(s) and life-threatening complications requiring management in a critical care setting (for close clinical monitoring and organ(s) support).[4] However, the admission of ACLF patients to the ICU is often considered inappropriate or even futile due the pre-conceived expectation of high mortality despite organ support. This old paradigm has been challenged by different investigations showing an improvement in the prognosis of critically ill patients with cirrhosis in recent years.[61,62] Clinical outcomes of patients with ACLF in the ICU are comparable to those observed in individuals without cirrhosis with similar baseline disease severity.[63] In a retrospective study conducted in ICUs that included 71 patients with ACLF and 142 patients without cirrhosis matched by type and severity of illness, ICU-mortality and hospital-mortality were similar between patients with and without cirrhosis (24% *vs.* 23%, respectively, for ICU-mortality, and 32% *vs.* 28%, respectively, for hospital mortality). Moreover, the CANONIC study showed that one fifth of patients with the most severe form of ACLF (ACLF-3) resolve the syndrome, that prognosis in these patients should be assessed after 3-7 days



	AUROC (95% CI)	*p* value *vs.* CLIF-C ACLF
CLIF-C ACLF	0.79 (0.73-0.85)	
MELD	0.70 (0.62-0.77)	0.0089
MELD-Na	0.70 (0.62-0.77)	0.0097
Child-Pugh	0.70 (0.63-0.77)	0.0075

Fig. 6. Accuracy of the CLIF-C ACLF score compared to the MELD score, MELD-Na score and Child-Pugh score in predicting 28-day mortality of patients with ACLF from the CANONIC study. Comparison of the AUROCs estimated for each score. The CLIF-C ACLF score showed a significantly higher predictive ability in comparison with all the other scores. ACLF, acute-on-chronic liver failure; CLIF-C, EASL-chronic liver failure consortium; MELD, model for end-stage liver disease. (Reproduced from[15]).

of full intervention and never at ICU admission and, finally, that early liver transplantation in ACLF 2-3 is associated with an undoubtable survival benefit.[2] Patients with ACLF 2-3 at day 3-7 who were transplanted early had a 6-month probability of survival of 80.9% compared to 10% in non-transplanted patients.[64] Together these data indicate that criteria for deciding ICU admission among patients with ACLF should not be different to those used for other populations and that denial of critical care in patients with cirrhosis who have organ failure(s) solely because of the existence of underlying cirrhosis is not justified.

Box 1 describes the main indications for ICU and intermediate care admission in patients with ACLF or other life-threatening complications. This table also details comorbid clinical conditions that are associated with poor short-term prognosis and that could thus be considered as a contraindication for critical care. Admission of these patients to the ICU should be considered on a case-by-case basis. Box 1 also describes the recommended time of admission, prognosis assessment (better established after some days of full critical care) and potential rules to maintain or withdraw organ support while patients are in the ICU. Tables S8 describes the recommended general ICU management in patients with ACLF.

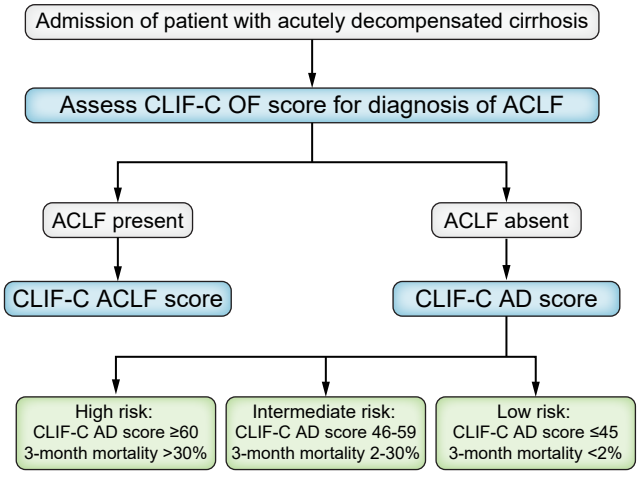


Fig. 7. Algorithm for the sequential use of the EASL-CLIF consortium predictive scores in patients with cirrhosis admitted to hospital with acute decompensation. ACLF, acute-on-chronic liver failure; AD, acute decompensation; CLIF-C, EASL-chronic liver failure consortium; OF, organ failure. (Reproduced from[60]).

Acute intrahepatic precipitants

Does treatment of HBV reactivation impact on the outcome of ACLF?

Recommendations

- Nucleos(t)ide analogues (NAs) should be started immediately in patients with HBV-related ACLF (**LoE 2, strong recommendation, strong consensus**).
- In patients with HBV-related ACLF, liver transplantation should be considered in those with a severe presentation (*e.g.*, MELD score >30; ACLF-2 or -3) despite early antiviral treatment initiation, particularly in the absence of early virologic response (<2-log reduction) and lack of clinical improvement (**LoE 2, strong recommendation, consensus**).

Statements

- In patients with HBV-related ACLF, the use of NAs reduces mortality (**LoE 2, strong consensus**).

Once ACLF develops in patients with spontaneous reactivation of HBV infection, the prognosis is poor with 3-month mortality rates without liver transplantation of around 50–55%.[65,66] There is now solid evidence that oral antivirals improve short-term survival in patients with ACLF due to HBV, such that they should be administered in all patients as soon as possible without waiting for the HBV DNA results. In a small (n = 27) randomised-controlled trial in patients with ACLF precipitated by spontaneous HBV reactivation, tenofovir improved 3-month survival compared to placebo (57% *vs.* 15%).[67] In one meta-analysis of antiviral therapy in ACLF due to spontaneous reactivation of HBV infection that included 11 randomised-controlled trials (including 654 patients; 340 treated with NAs, and 314 treated without NAs or placebo), NAs significantly increased 1-month survival (odds ratio 2.10; 95% CI 1.29–3.41; $p = 0.003$), and 3-month survival (odds ratio 2.15; 95% CI 1.26-3.65; $p = 0.005$).[68] Another meta-analysis on the impact of NAs in ACLF due to spontaneous HBV reactivation concluded that antiviral treatment with NAs significantly reduced 3-month

Box 1. Proposed criteria for admission to the ICU or another structure, assessment of the risk of death by 30 days, and potential rules for stopping organ support, all for patients with ACLF.

Indications for ICU admission

Indications

- Need for organ support (vasopressors, mechanical ventilation, or renal replacement therapy)
- Massive bleeding
- Grade III-IV hepatic encephalopathy (airway protection)
- Septic shock

Contra-indications to ICU admission

- Comorbidities associated with very poor prognosis
- Physiologically and/or biologically elderly patients[a]
- Severe pulmonary (GOLD criteria 3 or 4), cardiac (NYHA functional class III or IV) or neurological disease and ACLF-3
- Advanced neoplasm (life expectancy <6 months)
- Severe frailty[b] secondary to severe sarcopenia (muscle wasting and malnutrition)[c] or a Karnofsky performance status of 40 or less[d]

Time of ICU admission

- Within the first 6 h after diagnosis

Indications for admission at intermediate care structures

- Variceal bleeding
- Grade II-III hepatic encephalopathy
- Sepsis with AKI-HRS or with liver or coagulation failures

Assessment of the risk of death by 30 days

The risk of death should be evaluated 3-7 days after starting full organ support and not at admission

Potential rules for stopping organ support

The presence of 4 or more organ failures or a CLIF-C ACLF score >70 points 3-7 days after ICU admission should lead to a re-evaluation of the adequacy of maintaining organ support in the absence of liver transplant options

ACLF, acute-on-chronic liver failure; AKI-HRS, acute kidney injury-hepatorenal syndrome; CLIF-C, EASL-chronic liver failure consortium; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICU, intensive care unit; NYHA, New York Heart Association. [a]Unless being considered for liver transplantation or already listed. [b]Liver frailty score >4.4 or diagnosed by experienced physicians (eyeball test). [c]Severe sarcopenia defined by mid arm muscle area, bioelectrical impedance analysis, CT measure of psoas at L3 or diagnosed by experienced physicians (eyeball test). [d]Karnofsky performance status (40 = bedridden in more than 50% of the time; disabled; requires special care and assistance).

mortality (44.8 *vs.* 73.3%; relative risk 0.68; 95% CI 0.54-0.84; p <0.01) compared to no NA treatment.[69] Compared to ACLF caused by HBV reactivation, the efficacy of NAs in HBV-associated ACLF precipitated by other acute insults is unclear.[65]

Timing of treatment initiation seems critical in predicting the outcome of HBV-related ACLF. In a small study, an early profound reduction of HBV DNA was associated with a better outcome;[67] a more than 2-log reduction in HBV DNA levels at 2 weeks was found to be an independent predictor of survival. In support of an early initiation of treatment, a high MELD score (>30) has been reported to be independently associated with high short-term mortality (>90%) despite the use of antivirals.[70]

When considering the choice of nucleos(t)ide analogues, it appears that patients would benefit more from drugs with potent antiviral efficacy. Moreover, given the need for long-term use of NAs in survivors, drugs with a high resistance barrier, such as entecavir and tenofovir, are recommended. As AKI may occur in patients with ACLF, and tenofovir disoproxil fumarate has been reported to cause renal damage, tenofovir alafenamide could be used instead in patients with AKI.[71] Earlier studies found that despite a faster suppression of HBV replication, entecavir treatment was not associated with improved short-term survival compared to no treatment[72] and was associated with higher overall mortality compared to lamivudine treatment,[73] with lactic acidosis proposed as a possible cause of this increased mortality.[73] However, a recent review and meta-analysis reported similar short-term mortality between the entecavir and lamivudine groups,[74] and a randomised-controlled trial reported no survival differences between entecavir-, tenofovir disoproxil fumarate-, tenofovir-alafenamide-treated patients.[75]

Should patients with autoimmune hepatitis (AIH) and ACLF be treated with corticosteroids?

Recommendations

- In patients with AIH and ACLF, the benefit-risk ratio of the introduction of corticosteroid treatment should be evaluated on a case-by-case basis but corticosteroids should be avoided in case of concomitant uncontrolled infection (**LoE 5, strong recommendation, consensus**).
- If corticosteroids are administered to patients with AIH and ACLF, close surveillance for infection and strict monitoring of the efficacy of corticosteroid therapy should be performed (**LoE 2, strong recommendation, strong consensus**).

Statement

- Evidence for the role of corticosteroids in patients with AIH and ACLF is very limited (**LoE 5, strong consensus**).

ACLF may develop in patients with AIH because of hyperacute exacerbation of undiagnosed or misdiagnosed AIH, arbitrary cessation or tapering immunosuppressant therapy, and as a result of various secondary insults affecting the liver (*e.g.*, viral infection, drugs or toxic agents).[76] Corticosteroids can normalise hepatic inflammatory activity even in the cirrhotic stage. When considering treatment with corticosteroids, histological assessment is warranted to verify AIH with active inflammation.[77,78] Histology is also important since a significant proportion of patients with AIH presenting with ACLF (AIH-ACLF) can be seronegative. Moreover, from a clinical point of view, AIH-ACLF can be difficult to distinguish from autoimmune acute liver failure. However, histological features are distinct in the two entities.[79] A transjugular approach to obtaining a liver sample is strongly recommended when a severe coagulopathy is present.[77] Of relevance, a high proportion of patients with AIH-ACLF had a documented bacterial infection with sepsis at the time of hospital admission (*e.g.*, 76%[80]), which poses an obvious obstacle to the introduction of corticosteroid therapy.

Only two studies[81,82] have evaluated the role of corticosteroid therapy and clinical outcomes in patients with AIH-ACLF until now. Both used the APASL criteria to define ACLF and included a limited number of patients. A prospective study of 82 patients identified with AIH-ACLF in the AARC database[81] demonstrated that corticosteroid treatment is effective and safe in this patient population. Ninety-day survival was higher among patients who received corticosteroid treatment than among those who were not receiving corticosteroids and did not have baseline sepsis (75% *vs.* 48%, respectively; $p = 0.02$). The median length of ICU stay in the corticosteroid group was also significantly lower (1.5 *vs.* 4 days, $p < 0.0001$). Incidence of newly developed sepsis was similar in both groups ($p = 0.32$). However, in this study, a large proportion of patients (66%) were not eligible for corticosteroid therapy at baseline due to active sepsis, spontaneous bacterial peritonitis (SBP), history of active bleed, human immunodeficiency virus seropositivity or medically uncontrolled essential hypertension. In a retrospective dataset (n = 29),[82] a high frequency of infections (41.3%) was reported among patients receiving corticosteroids despite administration of prophylactic antibiotics.[79] Both studies found that a high MELD score (>27 and >24, respectively) was predictive of treatment failure, although a Child-Pugh score >11 had superior predictive ability.[82] These results potentially allow for early stratification of patients. Cautious follow-up changes in different parameters, such as MELD, MELD-Na, UK model for end-stage liver disease scores, bilirubin or INR during high-dose corticosteroid treatment might identify responders who will not need liver transplant. Improvement in one of these parameters within 4-7 days of corticosteroid therapy was associated with higher rates of response to corticosteroids in various studies of patients with acute severe AIH.[83–88] Accordingly, expert opinion suggests if no improvement in bilirubin or MELD-Na score is observed after 7 days of corticosteroid therapy in patients with in acute severe hepatitis, continuing the therapy might be futile, and patients should be assessed for liver transplantation due to high risk of progressing to ALF.[89]

Should patients with alcohol-related hepatitis and ACLF-2 or ACLF-3 be treated with corticosteroids?

Recommendations

- Corticosteroids are not recommended in patients with severe alcohol-related hepatitis and ACLF-3, nor in patients with uncontrolled bacterial infection (**LoE 3, strong recommendation, consensus**).
- If corticosteroids are administered to patients with severe alcohol-related hepatitis and ACLF, close surveillance for infection should be performed (**LoE 2, strong recommendation, strong consensus**).

Statement

- With increasing severity of ACLF, corticosteroid responsiveness is progressively reduced whilst the risk of infection increases (**LoE 2, strong consensus**).

In a single-centre cohort study, the prevalence of ACLF-2 or -3 in patients with biopsy-proven severe alcohol-related hepatitis was 32%.[88] The rates of response to corticosteroids were 42.6% for patients with ACLF-2 and 8.3% for those with ACLF-3 compared to 76.6% and 52.2% for patients without ACLF and those with ACLF-1 respectively. The very low probability of response makes the indication for corticosteroids questionable in patients with ACLF-3.

In a sub-analysis of the randomised placebo-controlled STOPAH trial, a Lille response was observed in 37.5% of patients with severe ACLF (*i.e.*, ACLF-2 or ACLF-3) receiving corticosteroids compared to 33% of those receiving placebo(a non-significant difference).[90] On the other hand, the presence of response (as defined by Lille model) was associated with a 90-day survival rate of 83.3% compared with 36.7% in the absence of response. It should be noted that patients on inotropic support and with creatinine >500 μmol/L were excluded from the STOPAH trial. Due to the small number of patients in the group with ACLF-3, we cannot conclude on the indication for corticosteroids in these patients.

Patients with severe alcohol-related hepatitis treated with corticosteroids have an increased incidence of serious infections (13%) compared to those receiving placebo (7%, $p = 0.002$).[91] In the subgroup of patients with ACLF-2 or ACLF-3, the rates of infection reach 33.1%.[90] Non-response to corticosteroids is associated with an increased risk of infection (83.3% *vs*. 57.7%) in patients with ACLF.[88] This infectious risk could counterbalance the hepatic effect of corticosteroids.

Acute extrahepatic precipitants

Variceal bleeding

Does transjugular intrahepatic portosystemic shunt (TIPS) placement improve outcomes in patients with variceal haemorrhage and ACLF?

Recommendations

- Both pre-emptive and rescue TIPS should be considered for patients with ACLF and variceal haemorrhage who do not have a contraindication for TIPS **(LoE 3, strong recommendation, strong consensus).**

Statements

- Variceal haemorrhage in patients with ACLF is associated with a very high probability of rebleeding (**LoE 3, strong consensus**).
- In patients with ACLF, the presence of hepatic encephalopathy should not be considered an absolute contraindication to TIPS (**LoE 4, consensus**).

ACLF in acute variceal haemorrhage. Acute variceal haemorrhage (AVH), which accounts for 70% of all upper gastrointestinal bleeding episodes in cirrhosis,[92] has been identified as a common cause of death in patients with cirrhosis, with a

6-week mortality rate of around 20%.[93] At present, progress has been made in the treatment of AVH, including endoscopic treatment, drug therapy, and TIPS placement, leading to decreased frequency of variceal bleeding over the last decade.[94] However, 10-20% of patients with AVH experience treatment failure after initial endoscopic and medical treatment, which is associated with a high short-term risk of further liver decompensation and death.[95] Several factors have been proposed to identify patients with AVH who are at high risk of poor outcomes and treatment failure, such as the MELD score, renal failure, bacterial infection and active bleeding at endoscopy.[93,96,97] Importantly, ACLF also significantly worsens outcomes in patients with AVH.[98,99] Indeed, ACLF almost doubles the risk of rebleeding, providing an easy identification criterion for patients with rebleeding risk.[98] Interestingly, ACLF predicted this independently of the presence of portal vein thrombosis, which is a well-known risk factor for rebleeding that has been described in several studies.[100,101]

TIPS for bleeding in ACLF. The Baveno Consensus conferences have recommended the use of pre-emptive TIPS placed within 24-72 hours in patients with Child-Pugh class B (>7) cirrhosis and active bleeding at endoscopy despite being on vasoactive drugs, and in patients with Child-Pugh class C (<14 points) cirrhosis,[102,103] since it improves outcomes.[95,104–107] Pre-emptive TIPS prevents rebleeding and ascites without increasing the risk of hepatic encephalopathy[108] and is thus a milestone in the treatment of patients with cirrhosis and AVH. The benefits of pre-emptive TIPS probably rely on the prevention of further deterioration after failure of initial treatment, avoiding a subsequent increase in rebleeding, organ failure and death.[109] This condition frequently meets the criteria of ACLF. AVH is a well-known trigger for the development of ACLF.[110,111] Two independent studies have demonstrated that TIPS, either pre-emptive TIPS or rescue TIPS, improves outcomes in patients with ACLF-1 or ACLF-2 and AVH.[98,99] It is noteworthy that patients with ACLF-3 were not included in these studies. Still there is a need to differentiate between pre-emptive TIPS and rescue TIPS in this collective of patients. The onset of renal failure or the need for renal replacement therapy often results in a very poor prognosis, especially in the context of rescue TIPS. In the case of pre-emptive TIPS, both short-term and long-term mortality could be halved in patients with ACLF. Therefore, and considering the marked impact of pre-emptive TIPS on rebleeding and most importantly short-term mortality, this therapeutic tool should be considered in the management of patients with ACLF and AVH, even in patients with bilirubin higher than 5 mg/dl.[98,99] The consequence would be to transfer the affected patients to hospitals with access to TIPS, thereby potentially reducing their mortality rate by 75%.[98] These data are nicely supported by a recent study which showed that the higher the MELD score, the bigger the survival benefit after pre-emptive TIPS.[112]

Bacterial and fungal infections

Do empirical antibiotic strategies tailored to the severity of infection and local epidemiology impact on the outcome of patients with ACLF?

Recommendations

- In patients with ACLF and suspected infection, empirical antibiotic treatment should be tailored according to the local epidemiology of bacterial infections and the presence of risk factors for antibiotic resistance (**LoE 2, strong recommendation, strong consensus**).
- In patients with septic shock or worsening of ACLF, broad-spectrum empirical antibiotics covering all potential pathogens should be used (**LoE 4, strong recommendation, strong consensus**).

A striking diversity exists in the epidemiology of bacterial infections in patients with cirrhosis across the world.[113] In the GLOBAL study, a large multicentre study in patients with cirrhosis and bacterial infections, infections due to multidrug-resistant organisms (MDROs) were more commonly observed in Asian centres: the percentage of infections due to MDROs exceeded 70% in Indian centres, compared to <20% in the USA, and 34% globally. Likewise, the rate of infections caused by extensively-drug resistant (XDR) bacteria was 33% in India, while it ranged from 0%–16% in all other areas.[114] However, the diversity that characterises the epidemiology of bacterial infections in patients with cirrhosis is made even more complex, since the pattern of antibiotic resistance is highly heterogeneous within a single country, state, region, and hospital, with marked differences in the type of MDROs and with an epidemiological scenario that could change over time.[115] It is quite well known that infections caused by MDROs are associated with lower resolution rates, higher incidence of septic shock and ACLF and higher short-term mortality compared to those caused by susceptible strains.[114] Bacterial infections, especially with MDR and XDR organisms, are associated with the highest risk of ACLF development, accounting for almost half of ACLF cases globally. The risk is particularly high in those with ascites, hepatic encephalopathy, poor liver function, a high MELD score, and in whom empirical antibiotic treatment has failed. In keeping with the heterogeneity in the epidemiology of bacterial infections in patients with cirrhosis, the development of ACLF occurs most commonly in the Indian subcontinent and less in Southern Europe. The common infections that can trigger ACLF include SBP and pneumonia. Patients who develop ACLF following a bacterial infection have high case fatality rates and are frequently unable to clear the infection.[116] However, the association between ACLF and bacterial infections is much more complex. In fact, bacterial infections may precipitate ACLF or develop during the course of ACLF. Bacterial infections can be detected in up to 44% of patients admitted to the hospital for acutely decompensated cirrhosis who then develop ACLF,[3] and in one-third of those admitted to the hospital with a diagnosis of ACLF.[117] Among the remaining patients with ACLF, approximately half develop bacterial infections within a follow-up period of 4 weeks. The severity of ACLF and its clinical course are significantly worse and mortality significantly higher in patients with bacterial infections than in those without. The type of infections, the presence of

sepsis or septic shock, and the isolation of MDROs also negatively influenced infection resolution and prognosis.[117] Thus, knowledge of the local epidemiology of bacterial infections (based on periodic reporting) is mandatory for prescribing an effective first-line empirical antibiotic treatment in patients with cirrhosis and is even more important in those with ACLF. Several studies proved that early administration of an appropriate first-line antibiotic treatment is associated with a reduction in mortality rate in patients with cirrhosis and bacterial infection, and that any delay is associated with an increase in mortality, particularly in patients with septic shock.[118] A proper empirical antibiotic treatment should cover all of the potential pathogens and thus should be based on the local epidemiology of bacterial infections and on the detection of risk factors for those sustained more frequently by MDROs, including prior antibiotic treatment, high MELD score, recent invasive diagnostic or therapeutic procedure. The environment where the infection developed, the severity of the infection, the type of infection, and the pharmacokinetics and pharmacodynamics of antibiotics should also be considered. Patients with ACLF, sepsis, severe sepsis or shock should receive empirical strategies covering all the potential pathogens. Consequently, since the rate of bacteria resistant to classic β-lactams now exceeds 50% in many centres, they are only recommended for community-acquired SBP, blood stream infections and urinary tract infections in patients without sepsis or ACLF, while their combination with antibiotics active against intracellular pathogens (azithromycin or quinolones) is recommended for patients with pneumonia.

Does early empirical antibiotic therapy impact on prognosis of infected patients with ACLF?

Recommendations

- Patients with ACLF and suspicion of bacterial infections should receive broad-spectrum, empirical antibiotic therapy according to local epidemiology as soon as possible (**LoE 3, strong recommendation, consensus**).
- In patients with ACLF and suspicion of bacterial infections, rapid and comprehensive infection workup is recommended (**LoE 5, strong recommendation, strong consensus**).

Several studies demonstrated that an early administration of an appropriate empirical antibiotic treatment is associated with a reduction in mortality rate in patients with cirrhosis and bacterial infections. Any delay in the initiation of a proper antibiotic treatment is associated with an increase in mortality, particularly in these patients, and especially in those with septic shock.[119,120] Patients showing a clinical response to empirical antibiotic treatment were the least likely to develop ACLF. A failure of the empirical antibiotic treatment is therefore frequently associated with the development of ACLF, to the extent that it becomes an independent predictive factor for its development.[116] The clinical course, the development of ACLF-2 or ACLF-3 at the final assessment and the probability of 90-day transplant-free survival are all worse in patients with ACLF and bacterial infection, either at diagnosis or during follow-up, than in those without a bacterial infection (45% *vs.* 70%, respectively). The negative impact of bacterial infections on 90-day-survival is particularly marked for patients with ACLF-1 and ACLF-2. The appropriateness of empirical antibiotic strategies has an impact on the clinical course and on the survival of patients with ACLF. Timeliness and adequacy of initial antibiotic strategies are associated with lower critical care requirements, better evolution of the syndrome in infection-triggered ACLF and lower 28- and 90-day mortality.[117] Early empirical antibiotic treatment should cover all of the potential pathogens but should balance this against the risk of selecting further antibiotic resistance.

Should early de-escalation of empirical antibiotics be instituted in patients with ACLF?

Recommendations

- Early de-escalation of empirical antibiotics (within a 24-to-72-hour time frame) is suggested to be applied in patients with ACLF receiving broad-spectrum antibiotics. De-escalation should be based on rapid microbiological tests and MDRO colonisation data (**LoE 5, weak recommendation, consensus**).

Broad-spectrum antimicrobials adapted to the local pattern of antibiotic resistance are recommended for the empirical treatment of patients with ACLF and infection.[113] This strategy minimises the risk of inadequate antimicrobial therapy and improves survival.[3,114] Carbapenems, glycopeptides, lipopeptides, lipoglycopeptides and new cephalosporins are prescribed to cover MDROs and in some centres XDROs. However, this antibiotic policy could promote further bacterial resistance, especially if antimicrobials are maintained for long periods. Antibiotic de-escalation, a key component of antimicrobial stewardship programmes, should be applied to prevent antibiotic resistance.[113] De-escalation consists of replacing broad-spectrum antibiotics with agents that have a narrower spectrum and stopping components of a specific antimicrobial combination. De-escalation should be performed early after the initiation of empirical antibiotic strategies, ideally within the first 24-72 hours.[121–123] The identification of the pathogen responsible for infection is pivotal for antibiotic de-escalation. Time to pathogen identification and associated sensitivities in clinical samples can take up to 5 days if only classical microbiological tests are used, resulting in prolonged exposure to broad-spectrum antibiotics. This delay affects the ability for physicians to promptly de-escalate to targeted anti-infective therapy and apply judicious antibiotic stewardship. The use of rapid microbiological techniques reduces this delay. Culture- and non-culture-based rapid techniques (MALDI-TOF MS [matrix-assisted laser desorption ionization-time of flight

mass spectrometry] and multiplex PCR among others) can be used to identify the pathogen(s) and define its antimicrobial susceptibility within 1 to 6 hours, thus facilitating rapid de-escalation.[113] If rapid microbiological techniques are not available, de-escalation could be based on epidemiological surveillance data in the absence of microbiological results from clinical samples. Recent studies show that the risk of infection by MDROs is very low in patients not colonised by resistant strains (6.8% *vs.* 40% in MDRO-carriers).[124] Antibiotic de-escalation seems to be safe but its real clinical impact in infected patients with ACLF deserves further investigation.[121–123]

Optimisation of antibiotic dosing through prolonged infusions and reduction of the duration of total antibiotic therapy (up to 7 days for most infections) are also an integral part of antimicrobial stewardship programmes aimed at improving clinical effectiveness while preventing new antibiotic resistance.[113,121]

Does empirical antifungal therapy impact prognosis in ACLF?

Recommendations

- Empirical antifungal therapy could be indicated in patients with ACLF developing a nosocomial septic shock who have additional risk factors for fungal infection (**LoE 5, weak recommendation, strong consensus**).

Invasive fungal infections develop in 1-5% of patients with decompensated cirrhosis (3-7% of culture-positive infections) and are more frequently observed in patients with ACLF, in whom they usually complicate the course of the syndrome.[113,117,125,126] Prevalence of invasive fungal infections in ACLF varies markedly among studies ranging from 1% to 47%, a finding that probably depends on differences in the severity of the syndrome, surveillance policies and diagnostic criteria.[127] Invasive candidiasis/candidemia is the most frequent fungal infection (70-90%) followed by invasive aspergillosis (10-20%). Patients with ACLF accumulate several risk factors for fungal infections including cirrhosis-associated immunodeficiency, broad-spectrum antibiotic exposure, multifocal colonisation, indwelling catheters, total parenteral nutrition, diabetes mellitus, prolonged ICU stay and renal replacement therapy.[113] Severe alcohol-related hepatitis and prolonged steroid therapy are well-known risk factors for invasive aspergillosis. In a prospective investigation that included 98 patients with biopsy-proven severe alcohol-related hepatitis, the incidence of invasive aspergillosis was 16%. In this study, risk factors for acquisition of invasive aspergillosis were ICU admission and a baseline MELD score ≥24 points.[128]

Though much more infrequent than bacterial infections, the impact of invasive fungal infections on prognosis is huge, with 28-day case fatality rates of 45-60% for invasive candidiasis and even higher for invasive aspergillosis.[113] Moreover, invasive fungal infections are a major contraindication for liver transplantation and therefore a frequent cause of delisting.

Current Surviving Sepsis guidelines recommend the empirical administration of antifungal therapy (mainly echinocandins) in patients with septic shock at risk of fungal infections.[129] Patients with ACLF and prolonged ICU stay fall into this population, especially if they are listed or in the process of being listed for liver transplantation. This empirical strategy should be followed by a rapid de-escalation if fungi are not identified. In that sense, two negative determinations of 1,3-β-D-glucan (an antigen present in the cell wall of many fungi including Candida) in blood samples can be used to safely discontinue antifungals.[113,130] The prognostic impact of prompt initiation of empirical antifungal therapy in this setting deserves further investigation.

Extracorporeal liver support

Do artificial or bioartificial extracorporeal liver support systems impact the outcome of ACLF?

Recommendations

- The routine use of artificial or bioartificial extracorporeal liver support or plasma exchange in ACLF is not recommended outside investigative trials **(LoE 2, strong recommendation, strong consensus).**

Statement

- Although albumin dialysis can improve the severity of hepatic encephalopathy, there is no evidence it improves the survival of patients with ACLF (**LoE 2, consensus**).

There are many devices that aim to artificially support liver function to bridge patients to liver transplantation and eventually allow for "recompensation".[131,132] Artificial devices remove protein-bound and water-soluble substances either by albumin dialysis (molecular adsorbents recirculating system [MARS] or single pass albumin dialysis), plasma separation and filtration (Prometheus), or by therapeutic plasma exchange (TPE). In turn, bioartificial systems contain hepatocytes to replace the functions of the failing liver (extracorporeal liver assist device [ELAD], HepatAssist). While promising, extracorporeal bioartificial livers able to completely replace liver function remain an unmet need. Data on the latter devices have yielded conflicting results regarding improvement of transplant-free survival in ACLF.[133,134]

From a theoretical point of view, artificial systems could benefit patients with ACLF by removing plasma cytokines and other drivers of the systemic inflammatory cascade typically observed in this setting. Substantial data have been generated in the literature assessing the efficacy and toxicity profile of

these devices in ACLF, including case series, prospective studies, randomised-controlled studies and systematic reviews and meta-analyses.[131,132,135] Unfortunately, the lack of uniform criteria for defining ACLF, the small sample sizes of most studies, the wide variability in disease severity and number of systems involved, as well as varying aetiologies, limit the quality and generalisability of the available data.

In the most recent individual patient data meta-analysis,[136] the authors assessed the effect of patient severity (ACLF grade) and treatment intensity (low-intensity therapy; standard medical care (SMT) alone or SMT plus ≤4 MARS sessions; high-intensity therapy; SMT plus >4 MARS sessions) on mortality. Three randomised-controlled trials were suitable for the meta-analysis, including a total of 285 patients (of whom 165 had ACLF). SMT plus MARS (irrespective of the number of sessions) did not improve survival compared with SMT alone, neither in the complete population nor in the analysis restricted to patients with ACLF. However, survival was significantly better among patients receiving high-intensity therapy than among those receiving low-intensity therapy (10-day survival, 98.6% *vs.* 82.8%, $p = 0.001$; 30-day survival, 73.9% *vs.* 64.3%, $p = 0.032$). Of note, although high-intensity therapy also increased survival in analyses restricted to patients with ACLF (10-day survival, 97.8% *vs.* 78.6%, $p = 0.001$; 30-day survival, 73.3% *vs.* 58.5%, $p = 0.041$), this effect was independent of the ACLF grade.

A recent systematic review reported a potential benefit of TPE, in both acute liver failure and ACLF.[137] In two out of four studies where plasma exchange-based liver support systems were compared to SMT for ACLF, a biochemical improvement was seen (coagulopathy, bilirubin, transaminases, or ammonia). In addition, 1- and 3-month survival in non-transplanted patients was improved in all four studies in patients with ACLF comparing plasma exchange *vs.* SMT (pooled odds ratio, 0.60; 95% CI 0.46–0.77; $p < 0.01$), As mentioned previously, studies were performed in Asia on mostly HBV-associated ACLF cases where the definition of ACLF does not require the diagnosis of cirrhosis and/or more than one organ failure.

The most recent network meta-analysis comparing and ranking different liver support systems and SMT in patients with ACLF (PROSPERO CRD42020155850) included 16 trials and assessed MARS, Prometheus, ELAD, TPE and BioLogic-DT.[135] Overall survival and transplant-free survival were assessed at 1 and 3 months. TPE significantly improved 3-month overall survival compared to SMT (relative risk 0.74; 95% CI 0.6-0.94) and ranked first on the cumulative ranking curves for overall survival outcomes, at 3 months and 1 month (surface under cumulative ranking curve [SUCRA], 86% at 3 months; and 77% at 1 month) and 3-month transplant-free survival (SUCRA, 87%). TPE ranked second after ELAD for 1-month transplant-free survival (SUCRA, 76%). Other comparisons did not reach statistical significance. The quality of evidence was moderate for TPE concerning 1-month overall survival and both transplant-free survival outcomes. Other results were of very low certainty.

Resuscitation for hypotension requiring vasopressor therapy

The online supplementary information provides recommendations, statements and companion texts related to the following four questions: i) "Does the use of albumin during the resuscitation process improve outcomes in patients with ACLF who require vasopressors for hypotension?; ii) "Is norepinephrine more effective and safer than vasopressin or its analogue terlipressin (continuous infusion) as the first vasopressor in patients with ACLF who require vasopressors for hypotension?"; iii) "Does a mean arterial pressure target of 65 to 70 mmHg improve prognosis in patients with ACLF who require vasopressors for hypotension?"; iv) "Do steroids (hydrocortisone 200 mg/day) improve outcome in patients with ACLF and refractory septic shock?"

Secondary infections

The online supplementary information provides recommendations, statements and information related to the following question: "Do bundles to prevent catheter-related infections and ventilator-associated pneumonia, that are currently used in general ICUs, improve prognosis in patients with ACLF admitted to the ICU?".

Immune modulators

Does granulocyte-colony stimulating factor (G-CSF) improve outcomes in patients with ACLF, regardless of white cell count?

Recommendations

- The routine administration of G-CSF is not recommended for patients with ACLF (**LoE 3, strong recommendation, strong consensus**).

Bone marrow-derived stem cells may be useful in modulating immune functions and promoting regenerative capacities in acute and chronic tissue injuries.[138,139] G-CSF mobilises haematopoietic stem and immune cells and has been evaluated as an alternative to exogenous stem cell infusions.[140,141] Two randomised-controlled single-centre trials in India and China used G-CSF in patients with ACLF and reported decreased rates of disease-related complications, such as bacterial infections, and improved survival.[142,143] Consequently, in India and China, G-CSF is being used as standard of care for ACLF, defined according to the APASL criteria which are different to the EASL-CLIF-C criteria. In Europe, a large multicentre randomised-controlled trial of G-CSF (GRAFT trial) was performed among patients with ACLF according to EASL-CLIF-C criteria.[144] This study was terminated early since G-CSF did not show a benefit (90-day transplant-free survival rate of 34.1% in the G-CSF arm compared to 37.5% in the SMT group), but led to severe adverse events in an interim analysis of 176 patients. This high-quality trial is in strong disagreement with the two previously described trials. Together, the available

evidence does not support the routine use of G-CSF CSF in patients with ACLF.

Nutritional support, sarcopenia, and frailty

Do nutritional support and rehabilitation improve outcomes in patients with ACLF?

Recommendations

Assessment

- Assessment of frailty using validated tools may be indicated in all patients with ACLF (**LoE 4, weak recommendation, strong consensus**).
- Screening of malnutrition using validated tools (*e.g.*, Royal Free Hospital Nutrition Prioritizing Tool) is indicated in all patients with ACLF (**LoE 3, strong recommendation, strong consensus**).
- Detailed evaluation of nutritional status in patients at risk of malnutrition should include:
  - a bedside assessment of energy requirement performed by a dietitian or by an expert in medical nutrition (**LoE 3, strong recommendation, strong consensus**);
  - sarcopenia assessment using the skeletal muscle index or psoas muscle area at the third lumbar vertebra, if a CT scan has been performed (**LoE 3, strong recommendation, strong consensus**);
  - the measurement of liver frailty index in non-bedbound patients (**LoE 4, weak recommendation, strong consensus**).

Target for nutrition and intake

- Target for energy is 30–35 kcal/kg/day (or 1-1.4x esting energy expenditure); target for protein is 1.2–1.5 g/kg/day (**LoE 4, strong recommendation, strong consensus**).
- Restriction of protein intake should be avoided, since it is detrimental in cirrhosis (**LoE 2, strong recommendation, strong consensus**).
- Oral intake should be preferred whenever possible; if oral intake is not possible, enteral nutrition ideally using a naso-jejunal tube should be attempted. If enteral nutrition is not tolerated, parenteral nutrition can be used as for other critically ill patients (**LoE 4, strong recommendation, consensus**).
- Micronutrients that should be supplemented if needed include vitamin A, folic acid, thiamine, pyridoxine, vitamin B12, vitamin D, vitamin E, iron, selenium, zinc, calcium, magnesium, phosphorous (**LoE 4, strong recommendation, consensus**).
- In patients fasting for >12 hours (including nocturnal fasting), intravenous glucose at 2-3 g/kg/day can be recommended (**LoE 4, weak recommendation, consensus**).

Controls required and special situations

- Refeeding syndrome should be monitored, prevented, and treated as early as possible (**LoE 4, strong recommendation, strong consensus**).
- In patients who experience variceal bleeding/upper gastrointestinal bleeding, oral nutrition should be started as soon as possible. Enteral nutrition can be used safely (**LoE 1, strong recommendation, strong consensus**).

The prevalence of frailty, a condition that refers to decreased physiologic reserve and increased vulnerability to health stressors mediated by several factors including malnutrition, sarcopenia (reduced muscle mass, strength, and function), and exercise intolerance, increases with declining liver function and has a significant impact on liver-related outcomes, including those related to liver transplantation.[145] More specifically, the prevalence of malnutrition in patients with decompensated cirrhosis is very high, affecting all patients with Child-Pugh class C cirrhosis.[146,147] Sarcopenia is also highly prevalent, with a reported prevalence ranging from 22% to 62% in patients with cirrhosis.[148]

Specific data in ACLF is lacking, but it can be speculated that most patients with ACLF are malnourished and sarcopenic. Cirrhosis is a catabolic state, and energy requirements further increase in patients presenting with clinical complications such as AKI and bacterial infections (*e.g.*, SBP).[146,147] The risk of malnutrition increases during hospitalisation, particularly in the ICU, and a large amount of data has proven that malnutrition is an independent risk factor for the development of bacterial infections, further decompensation, and death in patients with decompensated cirrhosis.[146,147] As such, malnutrition is a key target for therapy in decompensated cirrhosis and nutrition should be considered part of the standard of care in patients with ACLF.

In a meta-analysis, nutritional supplementation in hospitalised patients was not associated with reduced mortality.[149] However, most of the studies included patients with highly advanced liver disease and the interventions were very short. In a recent study, improvement in nutrition led to a reduction in decompensation-related readmissions.[150]

In the population of patients with cirrhosis, including those with ACLF, a detailed assessment of frailty, particularly nutritional status, should be performed with the aim of calculating resting energy expenditure. Dietitians/experts in medical nutrition should be involved in this step.

Given that addressing frailty in hospitalised patients with decompensated cirrhosis is a complex task, a combination of different methods can be proposed, including muscle strength assessment by bedside tools (*e.g.*, hand grip, liver frailty index[151] or clinical frailty scale[152]) and imaging tools (assessment of skeletal muscle mass at the level of the third lumbar vertebra on CT or MRI)[146,147] Unfortunately, patients with ACLF are often very sick, and not suited for most of these assessments. Given the low likelihood of it being affected by acute changes in functional performance and the high probability of having

previously available cross-sectional imaging data, assessment of sarcopenia is the preferred tool in the hospital setting.

In turn, screening of malnutrition should be done at admission according to existing tools (*e.g.*, Royal Free Hospital Nutrition Prioritizing Tool,[153] or the Subjective Global Assessment). In critically ill patients admitted to the ICU, specifically designed scores such as the Nutrition Risk in Critically ill score and its modified variant can be used and have been validated in patients with cirrhosis.[154,155]

The recommended calorie intake in critically ill patients with cirrhosis is 30–35 kcal/kg/day. The recommended protein intake in this population is 1.2–1.5 g/kg/day, which can be increased up to 2 g/kg/day in critically ill patients.[156]

It is important to note that renal replacement therapies affect metabolism and nutrient balance by inducing loss of water-soluble, low-molecular weight substances and nutrients, including amino acids (up to 10-15 g/day), and of proteins and vitamins (up to 10 g/day).[157]

In patients who can tolerate oral intake, this route is the preferred one and oral supplementation should be used when necessary. In patients who either do not tolerate the oral intake, have hepatic encephalopathy grade 2 or higher, or have their airways protected, medical nutrition using enteral (*i.e.*, through a feeding tube) or parenteral nutrition should be considered.[146,147]

Enteral nutrition is preferable to parenteral nutrition whenever possible and can be provided by either a naso-gastric tube or by a naso-jejunal tube. Transpyloric feeding through a naso-jejunal tube reduces the risk of aspiration compared to feeding through a naso-gastric tube, and this approach should be favoured in patients at high risk of aspiration. Enteral nutrition support should be started within 24–48 hours of the hospitalisation, with the aim of providing >80% of the estimated or calculated energy and protein requirements within 48–72 hours.

Parenteral nutrition should be used as a second-line treatment in patients who cannot be fed adequately by oral and/or enteral nutrition.

After starting the nutritional supplementation, refeeding syndrome, which is characterised by hypophosphatemia, hypokalemia and hypomagnesemia, should be prevented, recognised early, and treated, since it can lead to fatal complications. Risk factors for refeeding syndrome include alcohol abuse, and treatment with insulin and diuretics,[158] circumstances that are common in patients with ACLF.

Randomised-controlled trials in the setting of ACLF either related to physical rehabilitation or nutritional support are scarce, and data are heterogenous and limited by small sample sizes. On meta-analysis, nutrition did not improve survival in decompensated patients with cirrhosis or in those with severe alcohol-related hepatitis.[159] However, hepatic encephalopathy improved in patients who received nutrition supplementation.

Percutaneous endoscopic gastrostomy tube placement should be avoided in patients with decompensated cirrhosis since it is associated with a high risk of complications.[160]

Nutrition has been particularly studied in patients with severe alcohol-related hepatitis. In one randomised-controlled trial, enteral nutrition rich in branched-chain amino acids was compared to steroids.[161] The two groups had similar 1-month survival, but long-term survival was better in patients receiving enteral nutrition. In another randomised-controlled trial, patients received steroids plus conventional nutrition or intensive enteral nutrition for 14 days.[162] While no differences were observed in short-term outcomes, 6-month mortality was lower in patients on enteral nutrition. In addition, patients receiving <21.5 kcal/kg/day and <77.6 g protein per day had significantly lower survival rates.

In essence, while medical nutrition did not improve survival in this population on meta-analysis, a decrease in hepatic encephalopathy and shorter hospital stays have been documented, therefore supporting the recommendation to start oral nutrition as early as possible, with enteral nutrition being an alternative if the cough or swallow reflex are not intact.

As for immunonutrition, data are very scarce. In a recent open-label randomised-controlled trial in patients with ACLF, intravenous omega-3 fatty acids were safe and effective in reducing systemic inflammation, endotoxemia, and sepsis.[163]

There is no data regarding physical rehabilitation in the setting of ACLF, and this intervention, together with nutritional interventions, should be addressed by future studies.

Use of non-selective beta-blockers (NSBBs)

Should NSBBs be continued in patients with ACLF?

Recommendations

- In patients with ACLF, the decision to continue using NSBBs is suggested to be made on a case-by-case basis with careful dose titration based on close monitoring of the mean arterial pressure and renal function (**LoE 5, weak recommendation, consensus**)

Should NSBBs be initiated after the resolution of ACLF?

Recommendations

- In patients who recover from an episode of ACLF, NSBBs should be initiated cautiously, with close monitoring of blood pressure. Dose increases should be guided by the mean arterial pressure; below a threshold of 65 mmHg, beneficial effects are limited **(LoE 5, strong recommendation, consensus).**

Statement

- No specific study has addressed the safety and efficacy of starting NSBBs in patients who recover from an episode of ACLF. Therefore, the effect of NSBBs on outcomes is not known (**n.a., strong consensus**).

NSBBs were first used for the prevention of variceal bleeding over 40 years ago,[164] but since then, an improved understanding of their mechanisms of action has led to their wider use, including for the prevention of recurrence of variceal

bleeding and more recently for prevention of complications of cirrhosis.[165] However, a retrospective study conducted in patients with refractory ascites has shown that the risk of death was higher among those receiving NSBBs.[166] Another retrospective study conducted in patients with SBP has shown that the risk of death was higher among those who were prescribed NSBBs than in those who were not.[167] Experts from the Baveno VII workshop recommend that "In patients with ascites, NSBBs should be dose-reduced or discontinued in case of persistently low blood pressure (systolic blood pressure <90 mm Hg or mean arterial pressure <65 mm Hg) and/or hepatorenal syndrome (HRS)-AKI".[103] As patients with ACLF can be haemodynamically unstable and have renal dysfunction, the ongoing use of NSBBs can be deleterious. Therefore, in many cases, NSBBs are either stopped or their dose is reduced. In the CANONIC study, in about 50% of patients with ACLF (n = 78 of a total of 155 patients that were on NSBBs at admission) who were already being treated with NSBBs, the drug was stopped after hospitalisation and the dose was reduced in a further 8 of the 77 patients that continued to receive NSBBs.[168] However, there are two specific studies in patients with ACLF that provide circumstantial evidence that NSBBs may be useful for these patients. The first study is based on analysis of 349 patients with cirrhosis and ACLF who were among patients of the CANONIC cohort. Of these 349 patients, 155 were already being treated with NSBBs before admission whereas the remaining 194 were not receiving the drug.[169] The group on NSBBs had less severe ACLF on admission and their 28-day mortality was significantly lower. The median dose of NSBBs administered was relatively low (40 mg propranolol; 111 patients [67.7%]; 12.5 mg carvedilol; 16 patients [10%]). In another study of 624 patients with acutely decompensated cirrhosis, 254 patients with ACLF were studied whilst on therapy with NSBBs (107 patients) or not (n = 147 patients).[170] In the whole cohort of 624 patients, median doses were 30 mg/day for propranolol (147 patients; 58%) or 12.5 mg/day for carvedilol (108 patients; 42%). Intake of an NSBB was associated with increased 28-day transplantation-free survival ($p = 0.004$). NSBB intake remained a positive prognostic factor even after adjusting for several potential confounders in the multivariable model (hazard ratio, 0.578; $p = 0.031$). They also observed that stopping NSBBs during admission was associated with lower survival. Finally, they observed a cut-off of 65 mmHg as the threshold for the beneficial effect of NSBBs. Together these findings indicate that studies designed to investigate the safety and efficacy of continuing NSBBs in patients with ACLF are needed. Of note, there is no data on whether the introduction or reintroduction of NSBBs in patients who recover from ACLF is associated with beneficial effects nor on the most appropriate time for NSBB reintroduction in this context. Nevertheless, because NSBBs influence the severity of systemic inflammation, possibly through effects on gut permeability and translocation, which may underlie the expanded use of this treatment,[165,169] it seems logical that NSBBs should be restarted as soon as possible after the recovery of patients from an episode of ACLF. Interestingly, for patients with decompensated cirrhosis in whom NSBBs have been stopped or dose-reduced, experts from the Baveno VII workshop recommend that NSBBs can be re-initiated or re-titrated "once blood pressure returns to baseline and/or HRS-AKI resolves".[103] Obviously, studies should be performed among patients with ACLF in whom NSBB therapy has been stopped.

Liver transplantation

Does liver transplantation improve survival in patients with severe ACLF (ACLF-2, ACLF-3)?

Recommendations

- An early assessment for liver transplantation should be proposed for all patients with severe ACLF (ACLF-2 or -3) (**LoE 2, strong recommendation, strong consensus**).

Statements

- Liver transplantation is associated with a clear survival benefit in patients with severe ACLF, but the limits of patient suitability are unknown (**LoE 2, strong consensus**).
- Liver transplantation of patients with severe ACLF is associated with a substantial increase in resource utilisation (**LoE 3, strong consensus**).

A prospective European observational study demonstrated that deceased-donor liver transplantation in patients with ACLF-2 or -3 was associated with a drastic improvement in survival compared to no transplantation (95% *vs.* 23%, respectively at 28 days, 90.5 *vs.* 12.5%, respectively at 90 days).[64] These observations were confirmed by other independent retrospective studies. A study from three French liver transplant centres reported that 73 patients with ACLF-3 received deceased-donor liver transplantation with an outstanding 1-year post-transplant survival of 84% compared to 8% for matched non-transplanted critically ill patients.[171] They observed a 1-year post-transplant survival that was not statistically different for patients with ACLF-2 (86%), ACLF-1 (82%) and without ACLF (90%). Four other studies confirmed these results with a 1-year post-transplant survival between 79% and 84% for patients with pre-transplant ACLF-3.[172–175] These impressive results come from retrospective studies and are presumably related to the careful selection of patients with ACLF-3.

Beside the unquestionable survival benefit related to liver transplantation in patients with ACLF-2 or -3, this surgical procedure is associated with a high rate of complications. In the study by Artru *et al.,* despite a 1-year post-transplant survival rate of 84%, all transplanted patients experienced complications (hepatic vascular and biliary tract complications) and 81% developed post-transplantation-acquired bacterial infections, 35% viral infections and 15% fungal infections.[171] Patients with ACLF-3 more frequently require prolonged

Box 2. Standard operating procedure for ACLFLT programme in the UK.

The ACLFLT programme

1. ACLFLT is a pilot programme implemented by the National Health Service Blood Transfusion service by which select patients with cirrhosis may be waitlisted in a prioritised waitlist tier that recognises both their high likelihood of death without liver transplantation and of deterioration such that transplantation would not be possible if they follow the standard process for elective transplantation
2. In terms of priority, the ACLF tier is below that of super-urgent priority, hepatoblastoma, splitable grafts and critically ill paediatric recipients
3. The expectation is for 1-year survival of >60% in patients receiving organs in this category

Entry criteria

Inclusion criteria

- Cirrhosis
- Severe organ dysfunction or failure requiring intensive care support with expected 28-day survival of <50% usually indicated by the presence of ACLF grade 3 according to the criteria
- Standard guidance applies to patients with underlying alcohol-related liver disease. Patients with alcohol-related hepatitis are not eligible for entry into this pathway

Exclusion criteria

- Severe chronic co-morbidity which would preclude LT
- Age >60 years
- Previous liver transplantation
- Active bacterial or fungal sepsis
- CMV viraemia
- Severe irreversible brain injury
- MOF of such a severity and/or with adverse trajectory precluding successful LT
- Use of ECMO
- Gross frailty and likely inability to rehabilitate
- Active malignancy
- Severe acute pancreatitis or intestinal ischaemia

Requirements prior to registration

- Local multidisciplinary team review and agreement
- Proposed case reviewed by independent reviewers (appointed by NHSBT/Liver advisory group).

If appropriate, the patient will be listed in the special ACLFLT category

ACLF, acute-on-chronic liver failure; ACLFLT, ACLF LT tier; CMV, cytomegalovirus; ECMO, extracorporeal membrane oxygenation; LT, liver transplantation; MOF, multiple organ failure. Courtesy of Professor William Bernal and Professor Douglas Thorburn based on the NHSBT Liver Advisory Group pilot service evaluation of liver transplant for ACLF.

intubation and renal replacement therapy in the post-transplant period.[175] Due to this rate of complications, the ICU and total hospital lengths of stay are increased.[171,175] A retrospective North American study confirmed these results by showing that patients with ACLF-3 experienced more frequent acute cellular rejection, post-transplant bacterial infections and post-transplant need for renal replacement therapy for more than 2 days.[176] Based on the length of stay of this study, the costs associated with liver transplantation for ACLF-3 might increase by nearly four-fold compared to the costs of liver transplantation in patients without ACLF. Moreover, patients with ACLF-2 or -3 were more likely to be transferred to a rehabilitation centre after transplantation.

Should patients with severe ACLF (ACLF-2, ACLF-3) receive priority on the waiting list?

Recommendations

- Patients with ACLF-3 should be prioritised on a MELD(-Na)-driven waiting list to reduce the excess of mortality (**LoE 2, strong recommendation, consensus**).
- We recommend pilot programmes of prioritisation of patients with ACLF-3 on the waiting list (**LoE 5, strong recommendation, consensus**).

Statements

- Current allocation systems underestimate the waitlist mortality of patients with severe ACLF (ACLF-2 or -3) (**LoE 2, strong consensus**).
- Delaying liver transplantation for patients with severe ACLF (ACLF-2 or -3) increases the risk of waitlist and post-transplant mortality (**LoE 3, strong consensus).**

ACLF is a rapidly progressive syndrome, and the development of sepsis and irreversible multiple organ failures can compromise the eligibility for liver transplantation even on the waiting list. In a large retrospective European study, the 1-year intent-to-transplant survival from listing was 72% and 53% for patients with ACLF-2 and ACLF-3, respectively.[175] A study on the United Network for Organ Sharing (UNOS) database (about 79,000 listed patients) showed that patients with ACLF-3 had a higher probability of mortality within 1 year after listing compared to patients with a lower grade of ACLF and those without.[173] These mortality rates on the waiting list were observed in the context of an MELD- or MELD-Na-driven allocation system. UNOS data demonstrated that patients with ACLF-2 or 3 with relatively low MELD-Na scores (<25) had the highest waitlist mortality rates, ranging between 30-40%, suggesting the inability of MELD to adequately prioritise these patients. The implementation of the SHARE-35 rule (to give a broader access to liver transplantation for patients with MELD-Na ≥35) in the United States resulted in a significant reduction in 90-day waitlist mortality for patients with ACLF-3 but not in those with 4 or more organ failures, highlighting that SHARE-35 is inadequate for the sickest patients with ACLF-3.[176] Another study based on the UNOS database demonstrated that patients with ACLF-3 had higher 14-day waitlist mortality (28%) than patients listed with a status 1a (17%).[177] Altogether, these studies highlight that patients with ACLF-3 are misclassified on the waiting list by the MELD or MELD-Na scores, leading to excess mortality in this subgroup.

In a large prospective European observational study on 1,300 patients with acutely decompensated cirrhosis (CANONIC), the CLIF-C ACLF score, taking into account hepatic and extrahepatic organ failures, age and white blood cell count, outperformed the MELD and MELD-Na scores in the prediction of 28- and 90-day mortality.[15] A large US study from the Veteran Affairs (nearly 19,000 hospitalised patients with ACLF) confirmed that the MELD-Na score underestimated the

90-day mortality of patients with ACLF.[17] Moreover, early access to liver transplantation for patients with severe ACLF improves post-transplant outcomes. Indeed, in a UNOS study, performing a liver transplantation within the 30 days from listing, compared to beyond 30 days, for patients with ACLF-3 increased 1-year post-LT survival (82% *vs.* 79%).[173] A daily decrease in survival of 4-5% was observed on the waiting list during the first week of registration for patients with ACLF-3 if liver transplantation was not performed.[178]

In the UK, a pilot programme with a new allocation tier for patients with ACLF was started in May 2021 to try to resolve this problem of inequity (Box 2). This tier is just below the super-urgent patients. The required criteria include the presence of cirrhosis, significant liver failure manifested by jaundice and coagulopathy, organ failures necessitating organ support in the ICU or equivalent and a risk of 28-day mortality of >50%. These criteria would typically fit patients with ACLF-2 or -3.

Should criteria for futility of liver transplantation be used in patients with severe ACLF (i.e., ACLF-2 or ACLF-3)?

Recommendations

- The futility of liver transplantation of patients with ACLF-3 should be decided on a case-by-case basis considering independent predictors of post-transplantation mortality (**LoE 5, strong recommendation, strong consensus**).

Statement

- Defining criteria for futile liver transplantation in patients with ACLF-3 is an urgent medical need (**n.a., strong consensus**).

In the context of organ shortages, a strategy of rationing should be developed to maximise patient and graft survival. Despite the evident survival benefit of liver transplantation for patients with severe ACLF, progress should be made to limit the mortality of patients who are listed.

Some studies reported inadequate 1-year post-transplant survival (43%-46%) for patients with ACLF-3 or critically ill patients requiring multiple organ support; these findings suggest that not all patients with ACLF-3 are suitable candidates for liver transplantation.[179–181] Given donor organ scarcity, recipient criteria to define futile transplantation should be implemented to minimise post-transplant mortality. The classical futility scores (P-SOFT, balance of risk [BAR] and UCLA futility score) seem to be inaccurate to predict 1-year post-transplant survival in patients with ACLF-3.[171] Some authors suggest using criteria including active gastrointestinal bleeding, control of sepsis for less than 24 hours, haemodynamic instability requiring doses of norepinephrine >50 μg/min, and lung failure defined as a PaO_2/FiO_2 ratio <150, as criteria for futility, because each of them was associated with 1-year post-LT survival of <84%.[171] However, these criteria have not yet been prospectively validated. A large retrospective European study demonstrated that pre-transplant MDRO infections, arterial lactate at transplantation >4.4 mmol/L and need for renal replacement therapy at transplant were independently associated with post-transplant mortality.[175] In another retrospective multicentre study, Artzner *et al.* observed that four factors were independently associated with post-transplant mortality, including age ≥53 years, pre-transplant arterial lactate ≥4 mmol/L, mechanical ventilation with PaO_2/FiO_2 ratio ≤200 and pre-transplant leukocyte count ≤10 G/L.[174] They developed a simple model, called transplantation for ACLF-3 model (TAM), where the presence of each risk factor was associated with a score of 1 and the final TAM score was the sum. A TAM score >2 was associated with a 1-year post-transplant survival rate of only 8.3%. A TAM score >2 was validated in an independent cohort, wherein it was associated with a 1-year post-transplant survival rate of 10%. In addition, based on a retrospective study from 10 North American centres, the presence of portal vein thrombosis in patients with ACLF-3 was associated with a significant 1-year post-transplant survival reduction (57% *vs.* 92%).[181] Before implementing portal vein thrombosis as a futility criterion for liver transplantation in patients with ACLF-3, we need to confirm these observations and obtain more detailed data about the type (partial/complete), the date (acute/chronic) and the extension of the thrombus. All available data on independent risk factors for post-LT mortality come from retrospective studies. Before implementing futility rules, we need prospective studies that specifically address this issue.

In 2021, 35 experts tried to reach a consensus to define futility or inappropriateness of liver transplantation for critically ill patients with cirrhosis. The majority of experts stated that some risk factors could be used to define limits of transplantation, including severe frailty (defined by a clinical frailty scale ≥7), ongoing sepsis except for urinary tract infections, previous infection with pan-drug resistant bacteria, a respiratory failure with PaO_2/FiO_2 ratio <150, a circulatory failure requiring a dose of norepinephrine >1 μg/kg/min, arterial lactate >9 mmol/L and worsening clinical course.[182]

Should extended criteria organs be used for liver transplantation in patients with ACLF?

Recommendations

- Extended criteria donor livers should be considered for listed patients with ACLF-3 to reduce mortality on the waiting list (**LoE 4, strong recommendation, consensus**).

Extending donor selection criteria is a solution to organ shortages and is associated with a reduction in waitlist mortality. Though there is no universally accepted definition, numerous donor characteristics (advanced age, hypernatremia, steatosis, among others) are used to define extended criteria donor grafts, which were previously named marginal livers. Such grafts are associated with unfavourable post-transplant outcomes. Eurotransplant defines grafts as extended criteria donor livers when the donor meets one or more of the following criteria: age >65 years, ICU stay with ventilation >7 days, body mass index >30, macro-steatosis >40%, serum sodium >165 mmol/L, alanine aminotransferase >105 U/L, aspartate aminotransferase >90 U/L, serum bilirubin >3 mg/dl, donors after cardiac death or euthanasia. Scores have been developed to quantify the risk of graft

failure by using these extended criteria donors, *i.e.*, donor risk index (DRI) and BAR score. The latter takes into account donor and recipient characteristics (recipient MELD score, cold ischaemia time, recipient and donor age, previous transplantation, and use of pre-transplant life support) highlighting the important interaction of donor and recipient status in the prediction of post-transplant outcomes.[183] In the UNOS experience, patients with ACLF-3 who received younger donor organs with less comorbidities, more frequently from a donor with a head trauma, and less frequently a high-risk organ (DRI ≥1.7) had an adequate 1-year post-transplant survival of 82%.[173] In the same cohort, the use of a marginal donor organ (DRI ≥1.7) for patients with ACLF-3 decreased significantly 1-year post-transplant survival (78% *vs.* 83%, respectively). Yet, the survival benefit of liver transplantation is maintained in patients with ACLF-3 even if the transplanted liver comes from a marginal donor. Due to the need to perform an early liver transplantation in this subgroup of patients, there are no objective arguments against the use of extended criteria donor organs. Another study based on the same database demonstrated that accepting early extended criteria donor livers is essential to decrease the mortality rate on the waiting list, particularly for patients with ACLF-3 and 4-6 organ failures.[178]

Static cold storage is the conventional method of organ preservation characterised by a prolonged hypothermic ischaemic period contributing to the risk of early graft dysfunction, primary non-function and ischaemic cholangiopathy. Extended criteria donor livers are particularly susceptible to the deleterious effects of this type of storage. Both hypothermic and normothermic machine perfusion techniques have been shown to improve the outcomes achieved with extended criteria donor grafts.[184,185] The impact of these machines on post-transplant outcomes in patients with ACLF-3 is currently unexplored.

Should living donors be considered for liver transplantation in patients with ACLF-3?

Recommendations

- Living donor liver transplantation should be considered for patients with ACLF-3 in experienced centres (**LoE 2, strong recommendation, consensus**).

Another option to increase the donor pool for patients with ACLF is to perform liver transplantation from living donors. The use of living donor liver transplantation is associated with other advantages, including reduced waiting times and optimisation of surgical timing. Overall, living donor liver transplantation is associated with good results in highly expert centres. It is mostly performed in Eastern countries while the frequency of living donor liver transplantation in Western countries is very low (around 4-7% of transplants in Europe).[186] The donor mortality rate is around 0.2% to 0.5% (maybe underreported) and complications (biliary complication, hepatic artery and portal thrombosis) are reported in up to 78% of cases using right lobe donation.[187–189] The possibility of donor death, the higher rate of perioperative complications and the safer alternative of liver transplantation from deceased donors are the primary explanations for the low frequency of living donor liver transplantation in Western countries over the past several years.

Performing living donor liver transplantation in an emergency setting, *i.e.* ACLF, adds several other challenges. The time to evaluate the donor's spontaneous willingness to donate is clearly reduced. Pressing donor assessment raises special concerns about donor coercion. An expedited assessment could increase perioperative complications and psychological problems of donors.

The published results of living donor liver transplantation in the context of ACLF are scarce for patients with ACLF-3. One experience from Hong Kong reported that, in patients, the transplantation of a living donor *vs.* deceased donor liver graft did not affect the outcome, with an overall 1-year survival rate of 77%.[190] Other eastern studies of living donor liver transplantation in patients with ACLF-3 reported 1-year survival rates of 67% to 76%.[191–193] In one of these publications, the authors observed that right lobe procedures were associated with better 6-month post-transplant survival than left lobe procedures (100% *vs.* 25%, respectively).[191] Severe post-transplant complications (Clavien-Dindo ≥IIIb) were experienced by 25% to 33% of patients with ACLF (significantly higher than in patients without ACLF) and in 56% of patients with ACLF-3.[191–193]

Conclusions

ACLF is now recognised as a distinct clinical entity associated with a high risk of short-term death. The main principle for the management of ACLF is to diagnose and treat acute precipitants and provide organ support. Three questions should be urgently addressed in the field. First, the mechanisms of systemic inflammation, which is the driver of ACLF, should be investigated to identify targets for novel therapeutic approaches, in particular for patients who develop ACLF without any clinically apparent precipitant. Second, most of our knowledge on the management of patients with ACLF is based on studies involving critically ill patients without cirrhosis. Therefore, interventions for which clinical equipoise exists in patients with ACLF should be identified in order to design useful randomised-controlled trials. Third, studies should address the difficult question of criteria to define futility of liver transplantation in patients with ACLF-3, as robust criteria would impact the medical management of these patients.

Appendix. Delphi round consensus on the statements and recommendations of the present CPGs.

Recommendation/statement	Consensus
Both patients with prior decompensation and those without should be included in the definition of ACLF **(LoE 2, strong recommendation).**	100%
Organ failures as included in the EASL-CLIF-C criteria should be used for the diagnosis of ACLF **(LoE 2, strong recommendation).**	94%
The failure of one or more of the six major organ systems according to the EASL-CLIF-C criteria should be used to define the severity of ACLF and the risk of 28-day mortality **(LoE 2, strong recommendation).**	97%
The risk of 28-day mortality in a patient with ACLF should be assessed sequentially to evaluate their response to intervention **(LoE 2, strong recommendation).**	88%
Failure of the liver, kidneys, brain, coagulation, circulation, and/or respiration, as defined by the CLIF-C OF scoring system, confers a high case fatality rate at 28 days in patients with acutely decompensated cirrhosis **(LoE 2).**	100%
The number of organ failures according to the CLIF-C OF score that are simultaneously present is associated with increasing case fatality rate at 28 days **(LoE 2).**	100%
The CLIF-C OF score, as part of the CLIF-C ACLF score and ACLF grade, has been validated for sequential use and can be used repeatedly to determine the risk of 28-day mortality **(LoE 2).**	97%
The CLIF-C OF score has been validated in many countries around the world **(LoE 2).**	97%
The NACSELD classification for the diagnosis of ACLF underestimates the risk of death of patients with acutely decompensated cirrhosis. Therefore, the NACSELD score underestimates the 28-day and 90-day mortality of patients with acutely decompensated cirrhosis **(LoE 2).**	96%
The AARC (APASL ACLF research consortium) score is applied to patients diagnosed as having ACLF using the APASL criteria. As the APASL criteria underestimate the risk of death of patients with ACLF diagnosed using the EASL-CLIF-C criteria, the AARC score also underestimates 28-day and 90-day mortality in these patients **(LoE 2).**	93%
Every patient who is admitted for ACLF, or who develops ACLF during hospital stay, should undergo a systematic workup (summarised in Fig. 3) that seeks to identify the commonest precipitants, which include proven bacterial infection, alcohol-related hepatitis, gastrointestinal haemorrhage with haemodynamic instability, flare of HBV infection, hepatitis E virus infection, recent use of a drug known to cause cerebral failure, and recent use of a drug known to cause kidney failure **(LoE 2, strong recommendation).**	100%
Patients in whom the systematic workup fails to identify the presence of precipitant(s), among those that are expected, should undergo a case-by-case assessment, depending on the clinical context and based on a comprehensive list of all potential uncommon precipitants (Table 4) **(LoE 5, strong recommendation).**	97%
A precipitant of ACLF is an acute intrahepatic or extrahepatic insult that may cause organ dysfunction **(LoE 2).**	100%
The number of precipitants that are simultaneously present is a major determinant of the short-term outcome of patients with ACLF **(LoE 2).**	97%
In the patients without ACLF, the CLIF-C AD score should be used sequentially to provide prognostic information regarding 90-day, 180-day and 365-day mortality **(LoE 2, strong recommendation).**	97%
CLIF-C AD score, model for end-stage liver disease (MELD) score or MELD-Na score can be used to define risk of development of ACLF **(LoE 2, strong recommendation).**	94%
In patients with acutely decompensated cirrhosis and no ACLF, the CLIF-C AD score provides more accurate prognostic information than the MELD score, MELD-Na score, and the Child-Pugh score in predicting the risk o90-day, 180-day and 365-day mortality **(LoE 2).**	94%
CLIF-C AD score, MELD score and MELD-Na score have similar ability to predict the occurrence of ACLF and all perform better than the Child-Pugh score **(LoE 2).**	91%
In patients with ACLF, the CLIF-C ACLF score should be used sequentially to provide prognostic information **(LoE 2, strong recommendation).**	97%
In patients with ACLF, the CLIF-C ACLF score provides more accurate information + than the MELD score, MELD-Na score, and Child-Pugh score in predicting the risk of 28-day and 90-day mortality **(LoE 2).**	100%
Patients with ACLF requiring close monitoring or organ support + should be admitted to the ICU **(LoE 3, strong recommendation).**	100%
Admission of patients with ACLF and severe comorbidities to the ICU is suggested to be considered on a case-by-case basis **(LoE 5, weak recommendation).**	100%
Prognosis in patients with ACLF should be determined after 3-7 days of full organ support **(LoE 4, strong recommendation).**	97%
The presence of ≥4 organ failures or a CLIF-C ACLF score >70 points in individuals with no option for salvage liver transplantation are criteria to consider withdrawal of organ support and palliative care after 3-7 days of full organ support **(LoE 4, strong recommendation).**	97%
Criteria for deciding admission to the ICU for patients with ACLF are similar to those applied in the population of patients without cirrhosis since outcomes are similar when baseline clinical characteristics are similar **(LoE 4).**	84%
Nucleos(t)ide analogues (NAs) should be started immediately in patients with HBV-related ACLF **(LoE 2, strong recommendation).**	100%
In patients with HBV-related ACLF, liver transplantation should be considered in those with a severe presentation (*e.g.,* MELD score >30; ACLF-2 or -3) despite early antiviral treatment initiation, particularly in the absence of early virologic response (<2-log reduction) and lack of clinical improvement **(LoE 2, strong recommendation).**	94%
In patients with HBV-related ACLF, the use of NAs reduces mortality **(LoE 2).**	97%
In patients with AIH and ACLF, the benefit-risk ratio of the introduction of corticosteroid treatment should be evaluated on a case-by-case basis but corticosteroids should be avoided in case of concomitant uncontrolled infection **(LoE 5, strong recommendation).**	82%
If corticosteroids are administered to patients with AIH and ACLF, close surveillance for infection and strict monitoring of the efficacy of corticosteroid therapy should be performed **(LoE 2, strong recommendation).**	100%
Evidence for the role of corticosteroids in patients with AIH and ACLF is very limited **(LoE 5).**	97%
Corticosteroids are not recommended in patients with severe alcohol-related hepatitis and ACLF-3, nor in patients with uncontrolled bacterial infection **(LoE 3, strong recommendation).**	81%
If corticosteroids are administered to patients with severe alcohol-related hepatitis and ACLF, close surveillance for infection should be performed **(LoE 2, strong recommendation).**	100%
With increasing severity of ACLF, corticosteroid responsiveness is progressively reduced whilst the risk of infection increases **(LoE 2).**	100%
Both pre-emptive and rescue TIPS should be considered for patients with ACLF and variceal haemorrhage who do not have a contraindication for TIPS **(LoE 3, strong recommendation).**	100%
Variceal haemorrhage in patients with ACLF is associated with a very high probability of rebleeding **(LoE 3).**	100%
In patients with ACLF, the presence of hepatic encephalopathy should not be considered an absolute contraindication to TIPS **(LoE 4).**	91%
In patients with ACLF and suspected infection, empirical antibiotic treatment should be tailored according to the local epidemiology of bacterial infections and the presence of risk factors for antibiotic resistance **(LoE 2, strong recommendation).**	100%

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(*continued*)

Recommendation/statement	Consensus
In patients with septic shock or worsening of ACLF, broad-spectrum empirical antibiotics covering all potential pathogens should be used **(LoE 4, strong recommendation).**	97%
Patients with ACLF and suspicion of bacterial infections should receive broad-spectrum, empirical antibiotic therapy according to local epidemiology as soon as possible **(LoE 3, strong recommendation).**	94%
In patients with ACLF and suspicion of bacterial infections, rapid and comprehensive infection workup is recommended **(LoE 5, strong recommendation).**	100%
Early de-escalation of empirical antibiotics (within a 24-to-72-hour time frame) is suggested to be applied in patients with ACLF receiving broad-spectrum antibiotics. De-escalation should be based on rapid microbiological tests and MDRO colonisation data **(LoE 5, weak recommendation).**	97%
Empirical antifungal therapy could be indicated in patients with ACLF developing a nosocomial septic shock who have additional risk factors for fungal infection **(LoE 5, weak recommendation).**	97%
The routine use of artificial or bioartificial extracorporeal liver support or plasma exchange in ACLF is not recommended outside investigative trials **(LoE 2, strong recommendation).**	100%
Although albumin dialysis can improve the severity of hepatic encephalopathy, there is no evidence it improves the survival of patients with ACLF **(LoE 2).**	75%
In patients with ACLF and hypotension, human albumin or crystalloids should be used for initial fluid therapy **(LoE 4, strong recommendation).**[a]	94%
Human albumin is suggested for the treatment of patients with ACLF requiring substantial amounts of fluids and vasopressors **(LoE 5, weak recommendation).**[a]	91%
Based on data coming from the general intensive care unit (ICU) population, norepinephrine is the first-line vasopressor for patients with ACLF and hypotension unresponsive to fluid therapy **(LoE 4, strong recommendation).**[a]	100%
Dopamine is not recommended in patients with ACLF **(LoE 4, strong recommendation).**[a]	97%
Continuous infusion of terlipressin or vasopressin are potential second-line agents in patients with poor response to norepinephrine **(LoE 4).**[a]	94%
In patients with ACLF who require vasopressors for hypotension, we recommend a strategy to achieve a MAP ≥65 mmHg **(LoE 5, strong recommendation).**[a]	91%
Stress dose steroids may be used in patients with ACLF who require moderate or high doses of norepinephrine (>0.25 μg/kg/min) for hypotension **(LoE 3/4, weak recommendation).**[a]	91%
Relative adrenal insufficiency is highly prevalent in patients with ACLF and refractory septic shock, and is associated with poor outcome **(LoE 4).**[a]	94%
Bundles of measures aimed to prevent the development of catheter-related bacteraemia and ventilator-associated pneumonia should be used in patients with ACLF admitted to the ICU **(LoE 3, strong recommendation).**[a]	100%
Patients with ACLF admitted to the ICU are at high risk of nosocomial infections **(LoE 3).**[a]	100%
The routine administration of G-CSF is not recommended for patients with ACLF **(LoE 3, strong recommendation).**	100%
Assessment of frailty using validated tools may be indicated in all patients with ACLF **(LoE 4, weak recommendation).**	100%
Screening of malnutrition using validated tools (*e.g.*, Royal Free Hospital Nutrition Prioritizing Tool) is indicated in all patients with ACLF **(LoE 3, strong recommendation).**	100%
Detailed evaluation of nutritional status in patients at risk of malnutrition should include: - a bedside assessment of energy requirement performed by a dietitian or by an expert in medical nutrition **(LoE 3, strong recommendation);** - sarcopenia assessment using the skeletal muscle index or psoas muscle area at the third lumbar vertebra, if a CT scan has been performed **(LoE 3, strong recommendation);** - the measurement of liver frailty index in non-bedbound patients **(LoE 4, weak recommendation).**	97%
Target for energy is 30–35 kcal/kg/day (or 1-1.4x resting energy expenditure); target for protein is 1.2–1.5 g/kg/day **(LoE 4, strong recommendation).**	100%
Restriction of protein intake should be avoided, since it is detrimental in cirrhosis **(LoE 2, strong recommendation).**	100%
Oral intake should be preferred whenever possible; if oral intake is not possible, enteral nutrition ideally using a naso-jejunal tube should be attempted. If enteral nutrition is not tolerated, parenteral nutrition can be used as for other critically ill patients **(LoE 4, strong recommendation).**	94%
Micronutrients that should be supplemented if needed include vitamin A, folic acid, thiamine, pyridoxine, vitamin B12, vitamin D, vitamin E, iron, selenium, zinc, calcium, magnesium, phosphorous **(LoE 4, strong recommendation).**	91%
In patients fasting for >12 hours (including nocturnal fasting), intravenous glucose at 2-3 g/kg/day can be recommended **(LoE 4, weak recommendation).**	93%
Refeeding syndrome should be monitored, prevented, and treated as early as possible **(LoE 4, strong recommendation).**	100%
In patients who experience variceal bleeding/upper gastrointestinal bleeding, oral nutrition should be started as soon as possible. Enteral nutrition can be used safely **(LoE 1, strong recommendation).**	97%
In patients with ACLF, the decision to continue using NSBBs is suggested to be made on a case-by-case basis with careful dose titration based on close monitoring of the mean arterial pressure and renal function **(LoE 5, weak recommendation).**	79%
In patients who recover from an episode of ACLF, NSBBs should be initiated cautiously, with close monitoring of blood pressure. Dose increases should be guided by the mean arterial pressure; below a threshold of 65 mmHg, beneficial effects are limited **(LoE 5, strong recommendation).**	94%
No specific study has addressed the safety and efficacy of starting NSBBs in patients who recover from an episode of ACLF. Therefore, the effect of NSBBs on outcomes is not known **(n.a.).**	100%
An early assessment for liver transplantation should be proposed for all patients with severe ACLF (ACLF-2 or -3) **(LoE 2, strong recommendation).**	100%
Liver transplantation is associated with a clear survival benefit in patients with severe ACLF, but the limits of patient suitability are unknown **(LoE 2).**	100%
Liver transplantation of patients with severe ACLF is associated with a substantial increase in resource utilisation **(LoE 3).**	100%
Patients with ACLF-3 should be prioritised on a MELD(-Na)-driven waiting list to reduce the excess of mortality **(LoE 2, strong recommendation).**	90%
We recommend pilot programmes of prioritisation of patients with ACLF-3 on the waiting list **(LoE 5, strong recommendation).**	93%
Current allocation systems underestimate the waitlist mortality of patients with severe ACLF (ACLF-2 or -3) **(LoE 2).**	97%
Delaying liver transplantation for patients with severe ACLF (ACLF-2 or -3) increases the risk of waitlist and post-transplant mortality **(LoE 3).**	100%
The futility of liver transplantation of patients with ACLF-3 should be decided on a case-by-case basis considering independent predictors of post-transplantation mortality **(LoE 5, strong recommendation).**	100%
Defining criteria for futile liver transplantation in patients with ACLF-3 is an urgent medical need **(n.a.).**	100%
Extended criteria donor livers should be considered for listed patients with ACLF-3 to reduce mortality on the waiting list **(LoE 4, strong recommendation).**	93%
Living donor liver transplantation should be considered for patients with ACLF-3 in experienced centres **(LoE 2, strong recommendation).**	90%

a. Recommendation or statement whose companion text is provided in the online supplementary information.

Abbreviations

AARC, APASL ACLF research consortium; ACLF, acute-on-chronic liver failure; AD, acute decompensation; AIH, autoimmune hepatitis; AKI, acute kidney injury; APASL, Asia Pacific Association for the Study of the Liver; BAR, balance of risk; AVH, acute variceal haemorrhage; CLIF, Chronic Liver Failure; CLIF-C, CLIF consortium; CPGs, Clinical Practice Guidelines; COSSH, Chinese Group on the Study of Severe Hepatitis B; DRI, donor risk index; EASL, European Association for the Study of the Liver; ELAD, extracorporeal liver assist device; G-CSF, granulocyte-colony stimulating facto; ICU, intensive care unit; HBV, hepatitis B virus; INR, international normalised ratio; MAP, mean arterial pressure; MARS, molecular adsorbents recirculating system; MDRO, multidrug-resistant organisms; MELD, model for end-stage liver disease; NA, nucleos(t)ide analogue; NACSELD; North American Consortium for the Study on End-Stage Liver Disease; OF, organ failure; SBP, spontaneous bacterial peritonitis; SMT, standard medical care; SUCRA, surface under cumulative ranking curve; TAM, transplantation for ACLF-3 model; TIPS, transjugular intrahepatic portosystemic shunt; TPE, therapeutic plasma exchange; UNOS, United Network for Organ Sharing; XDR, extensively-drug resistant.

Conflict of interest

PA reports a patent with Biovie; receiving research grant from Gilead (Italy), travel grant from CSL Behring, lecture fees from CSL Behring, Kedrion, Grifols; and being on the advisory board for Biovie, Sequana Medical AG, Gilead (Italy), and Ferring. MB reports receiving research grant from Gilead; advisory board fees from Abbvie, Gilead, Intercept (advanz), Ipsen, Orphalan, Alexion, Deep Genomics; and lecture fee from Chiesi, Abbvie, Gilead, Orphalan, Alexion, Intercept (advanz). AB reports being consultant for Boehringer-Ingelheim. JF reports receiving lecture fees from Grifols. TG reports being on the advisory board for GoLiver Therapeutics and Cellaïon. RJ reports receiving grant support from the European Commission; lecture fees from Grifols; being on the advisory board for Yaqrit Ltd, Cyberliver Ltd, and Hepyx Ltd; a University license OPA, a novel treatment for hepatic encephalopathy to Mallinckrodt Pharma; and being founder of spinout companies, including Yaqrit Ltd., Cyberliver Ltd., and Hepyx Ltd. RM reports receiving consulting fees from Genfit, and CSL Behring. MP reports receiving research grants from Hungarian National Research, Development and Innovation Office (NKFI) and the European Commission; receiving lecture and/or consulting fees from Werfen, Boehringer Ingelheim RCV GmbH & Co KG, Danone Hungary Kft., Takeda Pharma Kft., Pfizer Kft., Ferring Pharmaceuticlas, Richter Gedeon Nyrt., eVisit Hungary Kft., Cassis Hungary Kft and SOBI. MT reports a travel grant from Grifols. All other panelists declare no competing interests. JT reports receiving grant support from the European Commission, lecture and/or consulting fees from Versantis, Gore, Boehringer-Ingelheim, Falk, Grifols, Genfit and CSL Behring. All other panelists report no competing interests.

Please refer to the accompanying EASL disclosure forms for further details.

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Supplementary data

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