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Acute decompensation of cirrhosis versus acute-on-chronic liver failure: What are the clinical implications?

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Abstract

It is essential to identify the subgroup of patients who experience poorer outcomes in order to adapt clinical management effectively. In the context of liver disease, the earlier the identification occurs, the greater the range of therapeutic options that can be offered to patients. In the past, patients with acute decompensation (AD) of chronic liver disease were treated as a homogeneous group, with emphasis on identifying those at the highest risk of death. In the last 15 years, a differentiation has emerged between acute-on-chronic liver failure syndrome (ACLF) and AD, primarily due to indications that the latter is linked to a less favorable short-term prognosis. Nevertheless, the definition of ACLF varies among the different knowledge societies, making it challenging to assess its true impact compared with AD. Therefore, the purpose of this review is to provide a detailed analysis emphasizing the critical importance of identifying ACLF in the field of advanced liver disease. We will discuss the differences between Eastern and Western approaches, particularly in relation to the occurrence of liver failure and disease onset. Common characteristics, such as the dynamic nature of the disease course, will be highlighted. Finally, we will focus on two key clinical implications arising from these considerations: the prevention of ACLF before its onset and the clinical management strategies once it develops, including liver transplantation and withdrawal of care.

KEYWORDS
cirrhosis, hepatitis, inflammation, liver, portal hypertension

INTRODUCTION

In the past 15 years, various definitions of acute-on-chronic liver failure (ACLF) syndrome have been put forth. However, their ultimate objective has been to distinguish a specific subset of patients who exhibit different natural history compared with presenting with an acute decompensation (AD) of cirrhosis. Distinguishing between ACLF and AD carries numerous clinical ramifications, in terms of prediction of the course of the disease, global disease management, and making timely referrals for liver transplantation (LT). This review aims to emphasize the ultimate clinical significance of distinguishing between ACLF and AD populations, with a specific focus on examining the documented evidence regarding the progression and outcomes of both conditions.

DIFFERENCES IN ACUTE-ON-CHRONIC LIVER FAILURE VERSUS ACUTE DECOMPENSATION: EAST VERSUS WEST

As per the World Gastroenterology Organization (WGO), acute-on-chronic liver failure (ACLF) refers to a clinical syndrome marked by the sudden deterioration of liver function (manifesting as jaundice and prolonged INR) along with the occurrence of one or more extrahepatic organ failures. It is associated with increased mortality rates within a period of 28 days to 3 months from its onset.[1] However, there are notable differences in the understanding of ACLF between Eastern and Western knowledge societies. According to the Asian Pacific Association for the Study of the Liver (APASL), ACLF identifies a homogeneous subgroup of patients with chronic liver disease or cirrhosis without any decompensation event, developing liver failure (defined by serum bilirubin ≥5 mg/dL and INR ≥1.4 or prothrombin activity <40%) secondary to an acute hepatic insult complicated within 4 weeks by clinical ascites and/or encephalopathy associated with high 28-day mortality.[2] The Chinese Group on the Study of Severe Hepatitis B (COSSH) also suggests that ACLF can develop in the presence or absence of cirrhosis.[3] In contrast, in their definition of ACLF the European Association for the Study of the Liver (EASL) and the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) include cirrhotic patients, regardless of their history of decompensation and consider both intra-hepatic and extra-hepatic insults. While extrahepatic organ failures are required to define ACLF, liver failure itself is not a mandatory criterion.[4,5] The Eastern approach to ACLF diagnosis generally involves patients with less advanced liver disease and fewer extrahepatic failures compared to the Western definitions. APASL-ACLF, in particular, resembles the definition of acute liver failure in individuals with chronic liver disease and has a higher chance of reversibility if survived (around 70%).[2] Hence, the APASL-ACLF diagnostic criteria highlights the disease's potential for reversibility, emphasizing patient's potential for recovery, promoting early diagnosis and creating opportunities for therapeutic intervention. In contrast, the EASL definition of ACLF encompasses nearly the entire population of patients with advanced liver disease with the highest short-term mortality risk. In fact, about 10% of ACLF patients meeting the criteria for APASL-ACLF are not captured by the EASL-ACLF criteria.[6] The observed lack of sensitivity seems to be associated with the utilization of a high bilirubin threshold to define liver failure. Lowering the bilirubin threshold could address the lack of sensitivity in the EASL definition, potentially improving the identification of patients at risk.[6] In contrast, the strict definition of APASL-ACLF may not identify all patients who exhibit a significant short-term risk of death and would likely be categorized as AD.[2,6]

According to the EASL definition, AD refers to the acute occurrence of one or more major complications of liver disease (ascites, hepatic encephalopathy (HE), gastrointestinal bleeding (GIB), or bacterial infection) in individuals with liver cirrhosis who do not meet the criteria for ACLF.[4] On the other hand, according to the APASL definition, all patients who are already experiencing decompensation and undergo a sudden deterioration of their condition (such as worsening ascites, HE, GIB, hepatorenal syndrome, or sepsis) would qualify as AD. As a result, the expected short-term mortality rate of APASL-AD patients is anticipated to be higher compared to that of EASL-AD patients.[2]

Despite these divergences, both Eastern and Western knowledge societies agree that ACLF and AD are associated with high short-term mortality risks (as high as 35%–40% at 28 days in the case of ACLF, regardless of the definition).[2,7,8] In both definitions, when extra-hepatic organ failures occur, they substantially worsen the patient's prognosis, justifying the inclusion of organ failures within the different grading systems.[2–5] The prevalence of the syndrome in patients hospitalized with AD is between 15% and 30% worldwide, while ACLF can develop in about 10% of patients during the hospitalization.[8] From a pathophysiological perspective, it is also acknowledged that ACLF is characterized by intense systemic inflammation (referred to as systemic inflammatory response or SIRS) and immunoparalysis. While the SIRS is related to hepatocytes damages and gut dysbiosis that lead to circulatory damage- and pathogens-associated molecular patterns (DAMPS and PAMPS) release, immunoparalysis is thought to be linked to an excessive compensatory anti-inflammatory syndrome.[8,9] The severity of systemic inflammation and immunoparalysis worsen with decompensated cirrhosis to ACLF, making the syndrome an ultimate expression of a dysregulated inflammatory response. Figure 1 is a schematic illustration of the relationship between APASL- and EASL-ACLF and the natural history of chronic liver disease.

Recent studies leveraging advancements in omics approaches, have provided a more comprehensive understanding of the pathophysiological mechanisms underlying ACLF and the distinctions between patients with ACLF and those experiencing AD.[10–15] This exploration encompasses multiple dimensions of complex interactions, including lipid and amino acid metabolism, inflammation, and mitochondrial function. Either through agnostic omics approaches or traditional hypotheses-driven investigations focused on specific inflammatory factors, the findings consistently indicate that ACLF exacerbates the disease beyond the baseline of AD.[16,17] Recent studies highlight distinctive markers capable of discerning AD from ACLF, including specific lipid features and mitochondrial dysfunction markers. In lipidomics-based studies, a unique plasma fingerprint distinguishing AD patient with ACLF was unveiled. It was specifically based on two lipid mediators, leukotriene E4 (LTE4) and 12-hydroxyheptadecatrienoic acid), both derived from arachidonic acid metabolism which is mainly associated with a pro-inflammatory response. Levels of these markers not only differentiate between AD and ACLF and different grades of ACLF but also positively correlate with markers of inflammation and non-apoptotic cell death.[10] Mitochondrial dysfunction, especially in circulating immune cells, is a hallmark of both AD and ACLF were evidence of dysfunctional fatty acid ß-oxidation and tricarboxylic acid cycle has been reported.[15] In the assessment of mitochondrial respiratory complex function in patients with AD and ACLF, it was observed that, compared to healthy controls, respiratory complexes functions

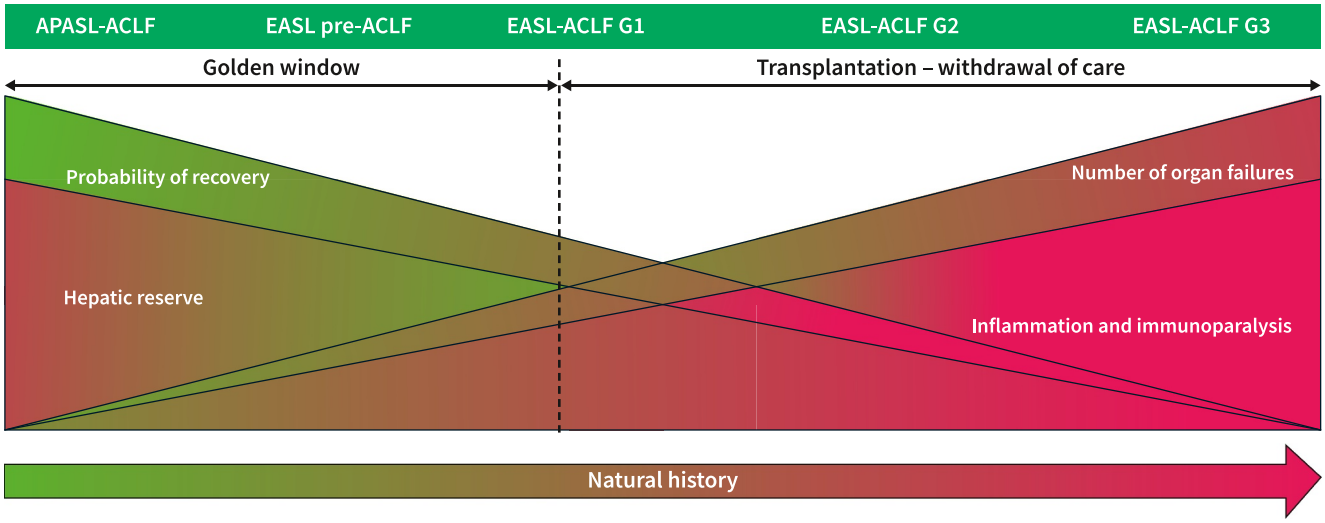

FIGURE 1 Diagram illustrating how Acute-on-Chronic Liver Failure is defined by both Asian Pacific Association for the Study of the Liver and European Association for the Study of the Liver. It outlines factors affecting recovery chances, such as hepatic reserve, inflammation, immunoparalysis, and organ failure. The diagram also highlights the "golden therapeutic window" for effective interventions.

deteriorated in both AD and ACLF.[18] This deterioration exhibited a continuous progression with the severity of the disease. Notably, ACLF patients (but not AD patients) specifically manifested dysfunction in mitochondrial complex IV. Although these indicators demonstrate a certain discriminatory capability between AD and ACLF, their predictive or diagnostic potential still requires clinical validation. From an immunological perspective, the progression from AD to ACLF is characterized by the progression of a compensatory anti-inflammatory response syndrome (CARS). CARS is associated with a pro-resolutive phenotype of immune effectors and a greater risk of septic events, one of the leading causes of mortality in patients with ACLF. Specifically, circulating monocytes and liver monocytes-derived macrophages exhibit a pro-restorative phenotype associating increased expression of anti-inflammatory markers (Mer Tyrosine Kinase receptor, CD163) in parallel with a decreased expression of human leukocyte antigen-DR, decreased phagocytic capacity and increased released of anti-inflammatory cytokines such as IL-10.[9,19–22] Research into the distinct pathogenic mechanisms of both conditions is an ongoing and challenging effort. Nevertheless, such evidence suggests a combined approach, including immune modulation, for treating ACLF.

CLINICAL COURSES OF ACLF

ACLF is a highly dynamic syndrome that undergoes rapid changes in its course, regardless of its definition. The clinical trajectory of EASL-ACLF has been assessed at various time points, revealing four distinct patterns: resolution, improvement, worsening, or steady/fluctuating. In a seminal study, nearly half of the patients showed improvement or resolution (49.2%), 30.4% had steady/fluctuating courses, and 20.4% experienced worsening.[23] Timely ACLF grading within the first week is crucial for accurate prognosis, as demonstrated by 81% of patients reaching their final ACLF grade before the 7th day. Similar findings were observed in patients with APASL-diagnosed HBV-ACLF.[24] In this study, 39.8% of patients showed a course toward resolution or improvement, while 25.8% followed a steady course with unchanged ACLF grades and 34.4% showed a worsening trajectory. In its princep study, daily calculation of the APASL ACLF research consortium (AARC) score during the first week showed mortality risk associated with score increments, especially with values exceeding 10.[25] Bilirubin and INR, demonstrated trends over time that aided in identifying different clinical courses, including rapid progression, slow progression, rapid recovery, slow recovery, and slow persistence accounting respectively for 25.6%, 16.8%, 30.2%, 18.3% and 9.1% of patients.[26] Overall, sequential evaluation of ACLF grades over time is essential to accurately adapt clinical management, as approximately 40%–50% of patients exhibit improvement or resolution, while others experience steady or worsening trajectories. The dynamic evaluation of EASL-ACLF assists in identifying the population that necessitates prompt decision-making regarding LT or the limitation of care.[27–30]

Importantly, in patients achieving EASL-ACLF grade 1 of EASL-ACLF within the first 3–7 days, 6-month mortality rate remains high (47%).[23] The prognosis was greater in patients who completely resolved EASL-ACLF with a 6-month survival rate 62%. This has been further confirmed by recent data showing that most patients (67%) who completely resolved EASL-ACLF were free at 1-year from any additional liver-related events.[31] The severity of ACLF episode as well as the type of organ failure may have an impact on the outcome. As an example, only 20% of patients mechanically ventilated in a context of ACLF are free from LT or death at 1 year.[32] According to APASL-ACLF, 70% of patients alive at 90-day were free from liver related events at 1 year.[2] Altogether, these data suggest that, until accurate identification of factors associated with a low-risk of events following an ACLF episode, it is recommended to refer patients to liver transplant centers

even if they show who show improvement or resolution of ACLF, given the significant remaining risk of death.

LIVER FAILURE AND UNDERLYING DISEASE STAGE IN THE COURSE OF THE DISEASE

ACLF can be classified into two types solely based on the symptoms observed at the onset of the disease, in terms of disease progression alone. One is liver failure, which can lead to the secondary development of multiple organ failure, and the other is mainly extrahepatic organ failure at the onset of the disease. APASL-ACLF patients typically present with bilirubin levels above 20 mg/dL and an INR of 2.5 or higher.[25,33] In this patient population, the occurrence of extrahepatic organ failures at presentation is rare (e.g., renal failure observed in only 5%–6% of cases). Conversely, EASL-ACLF individuals exhibit lower levels of bilirubin (usually between 10 and 15 mg/dL) and INR (ranging from 1.5 to 2.0).[4,6,23] As per EASL criteria, renal failure is the most frequently encountered organ failure (approximately 60% of patients), while liver failure is less common.[6] Besides, APASL- and EASL- conceptions differ in terms of the stage of underlying liver disease (compensated vs. decompensated). For instance, in the CANONIC study, 73% of patients had previously encountered episodes of decompensation.[7] To account for the potential influence of liver disease stage and previous decompensation, three subtypes of ACLF have been distinguished: Type A in patients with chronic liver disease without cirrhosis, Type B in patients with compensated cirrhosis and Type C in patients with decompensated cirrhosis.[1] Based on these consideration, it is suggested that the APASL-ACLF population display a higher likelihood of complete recovery with a better long-term prognosis than that of AD patients. In a recent study where patients with HBV-related APASL-ACLF were followed, the 90-day and 5-year mortality rates were very close (43.1% and 50.0%), suggesting that the long-term prognosis of APASL-ACLF survivors is good.[34] Similar findings were observed in an independent cohort of HBV-ACLF as defined by APASL.[35] Limited data are available regarding the long-term outcomes of the EASL-ACLF population, primarily due to its inherently poor prognosis. A prospective study found that previous AD was the most important factor affecting long-term outcomes following an EASL-ACLF episode independently of model for end-stage liver disease (MELD).[36]

CLINICAL IMPLICATION

Prevention

The differentiation of ACLF as a separate syndrome from AD has significant clinical implications. Firstly, it allows for the identification of a "golden window" for therapeutic interventions, focusing on patients who have the highest likelihood of benefiting from disease-modifying treatments. Secondly, it enables the recognition of distinct clinical trajectories, aiding in the management of patients in terms of LT candidacy and the decision to withdraw care when necessary.

Early detection of patients at risk of developing ACLF is crucial due to its prognosis. In outpatient settings, four simple predictors of EASL-ACLF were identified: MELD score, ascites, mean arterial pressure, and hemoglobin level.[37] Anemia has also been recognized as a marker for a higher risk of developing nosocomial ACLF in patients recently discharged from hospitalization for AD.[38] However, further research is needed to validate these findings and enable clinicians to effectively assess outpatient risk for developing EASL-ACLF. Additionally, investigations into the diagnostic value of clinically significant portal hypertension (through invasive or non-invasive means) are warranted to enhance the risk prediction of EASL-ACLF.

In patients hospitalized for AD, the PREDICT study identified three distinct clinical courses: pre-ACLF, unstable decompensated cirrhosis, and stable decompensated cirrhosis. Pre-ACLF patients, were charaterized by the development of EASL-ACLF within 3 months and exhibited higher MELD, Child–Pugh, and CLIF-C AD scores, as well as increased systemic inflammation markers such as leukocyte counts and C-reactive protein (CRP) compared to other groups.[39] Real-life cohorts have confirmed that the pre-ACLF phenotype is characterized by heightened systemic inflammation.[31,40] Notably, the Padua model, recently developed to predict the risk of ACLF in AD patients combines the CLIF-C AD score, Child–Pugh score, and CRP level, illustrating the weight of systemic inflammation in the risk of developping ACLF. This score has been further validated in a large independent cohort.[41] Patients with a Padua model greater than nine have a 45%–68% risk of developing EASL-ACLF within one year, with a median time to ACLF ranging from 28 to 58 days. These findings suggest that the severity of liver disease combined with systemic inflammation markers are the most reliable predictors of EASL-ACLF development in patients with AD. An optimization of the Padua model, referred to as Padua 2.0, has been recently developed. In this version, CRP was substituted with Presepsin (PSP), a soluble fragment of CD14, expressed by monocytes and macrophages, released during the inflammatory response. PSP demonstrated a stronger correlation with the risk of ACLF development compared with CRP.[42] The improved specificity of PAMPs-related inflammation is believed to account for the greater performance of Padua 2.0 compared to the Padua model. If further confirmed, the Padua and Padua 2.0 models could serve as important tools for identifying at-risk patients who require urgent evaluation for LT and for targeting a population suitable for the development of disease-modifying drugs. Studies investigating factors associated with APASL-ACLF (mainly in the setting of severe acute exacerbation of chronic hepatitis B infection) occurrence have also been conducted. They have identified that age, liver disease severity (bilirubin, prothrombin time, MELD score) or HBV viral load were associated with the risk of progression toward ACLF.[43–45] More recently, Dual-energy CT quantification of extracellular liver volume has been associated with such progression independently from liver disease severity parameters.[46] However, most of the predictive models are derived from single-center retrospective studies, and

further validation is needed. The therapeutic "golden window" refers to the ideal timeframe for initiating treatment in APASL-ACLF patients, which falls within 4 weeks of the onset of clinical symptoms. Early intervention during this window has shown significantly better outcomes, including reduced mortality rates and improved liver function.[2,47] Furthermore, EASL-ACLF grade I identify a subgroup of patients with the highest chance of recovery (approximately 50%) among the EASL-ACLF population.[4,8,23,27,48] In summary, the pre-ACLF, APASL-ACLF, and ACLF grade I conditions identify patient populations most suitable for evaluating potential disease-modifying drugs based on the pathogenesis of the syndrome (Figure 1).[49]

Once AD and ACLF have occurred, medical management is based on the treatment of precipitating events, the prevention and treatment of organ failure, as well as the discussion regarding eligibility of the patient to LT. An increasing body of evidence is also revealing hemostasis disruptions in AD and ACLF patients. Patients with acute kidney injury, bacterial infections, sepsis, or those progressing from AD to ACLF are at a higher risk of bleeding.[50] ACLF patients exhibit a hypocoagulable state compared with AD patients, which has inconsistently been linked to increased bleeding risk.[51–54] In cases of variceal hemorrhage, ACLF patients face a higher risk of rebleeding, independent of hepatic venous portal gradient.[55] Additionally, excessive or premature fibrinolysis is observed in ACLF patients and is associated with bleeding events.[50] Evaluating coagulation problems in AD or ACLF patients may be most effectively performed through sequential visco-elastics tests alongside routine coagulation markers. However, until more specific data on ACLF is available, interventions for ACLF patients will remain individualized and guided by clinical judgment, as there is currently no clear evidence linking hemostasis correction to improved outcomes or reduced bleeding risks.[50]

Managment

Many strategies targeting the pathophysiological mechanisms of AD and ACLF are currently under evaluation.[49] They specifically aim to mitigate systemic inflammation and liver damage, favor liver regeneration, regulate portal hypertension and modulate the microbiome. Some have already been reported to improve the outcome of patients with AD and ACLF. Albumin infusion has been shown to improve survival in selected patients with refractory ascites and transjugular intrahepatic portosystemic shunt (TIPS) insertion is associated with a decreased risk of further decompensation and death.[56,57] Notably, in the context of acute variceal hemorrhage, preemptive TIPS was associated with improved outcome even in the context of ACLF.[55] TIPS placement could either obviate the need of LT as well decrease the risk of death while on the waiting list and should be systematically discussed in its common indication.[58,59] During gastrointestinal bleeding episodes, prevention of ACLF development lies also on early introduction of antimicrobial therapy. Mitigation of infectious risk and early treatment of bacterial and fungal infection are of critical importance and help to prevent the occurrence of extra-hepatic organ failure regardless of the pattern of AD.[60–62] In the setting of severe alcohol-related hepatitis, steroids are the first-line agent to prevent further deterioration of liver function and death. However, a decreased probability of response to steroids is observed in severe ACLF grades and has been reported as low as 8% in patients with ACLF grade 3.[63] In Eastern countries, spontaneous reactivation of HBV infection is one of the most common precipitants for ACLF and is associated with high short-term mortality. Therefore, in case of AD, oral treatment with nucleos(t)ide analogs should be started as soon as reactivation is suspected.[62]

Among the novel most promising approaches is the combination of G-CSF treatment, which aim to increase liver-regeneration by mobilizing bone-marrow derived stem cell, and TAK-242, which aim to mitigate the TLR-4 mediated inflammation that is associated with the release of bone marrow derived cells. This combination has been demonstrated to improve the outcome of a murine model of ACLF and will be evaluated in a phase II study.[64] Besides, F-652 is a recombinant fusion protein of human IL-22 and immunoglobulin G2, which acts as an IL-22 agonist and activates signal transducer in liver parenchymal cells, enhancing tissue repair. In an open phase II study in alcohol-related hepatitis, it has been associated with an improvement of liver severity scores as well as with increased biomarkers of hepatic regeneration.[65] So far, the most advanced approaches in the ACLF setting are interventions based on extra-corporeal liver support (ECLS). ECLS, namely plasma exchange and a novel ACLF-specific device called Dialive®, target systemic inflammation and associated immune and albumin dysfunctions. Plasma exchanges are under evaluation in a large international phase III trial aiming to recruit 380 ACLF patients (NCT03702920), while Dialive® has been associated with improved outcome and biomarkers of severity in a recent phase II study.[66]

In the past decade, the sequential assessment of ACLF grades in patients with EASL-ACLF has become crucial for hepatologists and intensivists in their daily patient management. This assessment has important clinical implications for accurately predicting the patient's clinical trajectory. If there is improvement or resolution towards no-ACLF or ACLF grade 1 within the first week, the first step, as discussed earlier, is to refer the patient to an LT center. Indeed, these patients are at a significant risk of further decompensation and liver function deterioration, especially if they have a history of previous AD or were intubated during their stay in the intensive care unit.[32,36] Therefore, it is advisable to initiate a comprehensive pre-LT assessment once the ACLF episode has resolved or improved. Additionally, persistent severe EASL-ACLF (grades 2 and 3) identifies a subgroup of patients with a poor short-term prognosis, who should be evaluated for early LT. In this population, the survival probability at 28 days is as low as 0%–30%.[23,27,28] Over the last few years, there have been reports of favorable outcomes in critically ill patients (ACLF grade 3) following LT, with a 1-year survival rate often exceeding 80%.[67–72] However, the selection process for these patients is complex, with limited retrospective data and sample sizes.[48,73] The course of organ failure preceding LT, as assessed by

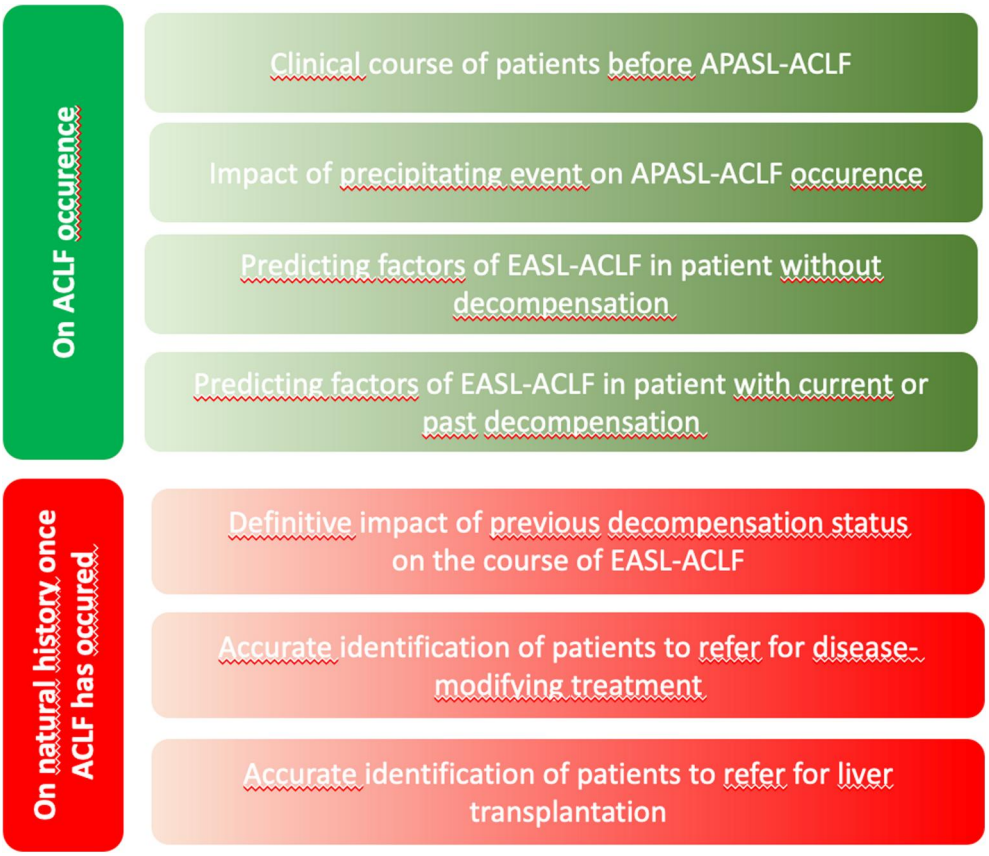

FIGURE 2 Areas of uncertainty in the natural history of acute-on-chronic liver failure syndrome.

EASL-ACLF grade, is a key parameter in optimizing outcomes.[74,75] For patients who are not eligible for transplantation, a persistent severe course of EASL-ACLF may indicate the appropriateness of withdrawing care[28,76,77] (Figure 1). However, withdrawing care is a complex decision, considering the irrevocable nature of the choice and the differing perspectives of caregivers and patient families regarding small survival probabilities. Balancing these factors while respecting the patient's life, dignity, and wishes presents statistical and ethical challenges, and a single score is unlikely to be the definitive determinant.[78]

As the reconciliation between Eastern and Western definitions of ACLF becomes less likely, further investigation based on APASL- and EASL- definitions of ACLF are required to comprehensively appreciate the determinants of outcome before and after ACLF including precipitating event TYPE. Additionally, with the increasing pipeline of potential disease-modifying treatments, there is an unmet need to accurately distinguish eligible patients for these treatments from those who should be referred for liver transplantation (Figure 2). Finally, despite initial data indicating that the clinical presentation and natural progression of events are not sex-specific in AD and ACLF, additional research is needed to validate this observation.[3,4,39,79–81] In any case, evidence is accumulating regarding the sex-specificity of clinical and biological markers of severity.[82,83]

CONCLUSION

Despite distinct approaches between the Eastern and Western definitions of ACLF, both groups exhibit a greater risk of short-term mortality compared to patients with AD. Two important clinical implications result from major studies investigating natural history of ACLF. Firstly, the recognition of a "golden therapeutic window" which encompasses APASL-ACLF, pre-EASL-ACLF, and possibly EASL-ACLF grade 1, where the potential benefits of disease-modifying interventions are maximized. Accurate identification within these groups of patients definitely candidates to such approaches is still to be determined. Secondly, the identification of distinct clinical trajectories that assist in the management of patients, including decisions regarding referring to liver transplantation, as well as determining the appropriate timing for withdrawal of care. As a reconciliation between Eastern and Western approaches becomes less likely over time, further investigation are needed to definitely identify predictors of APASL-ACLF, impact of precipitating event and history of decompensation on the occurence and course of ACLF.

AUTHOR CONTRIBUTIONS

Conception of the study, writing and critical appraisal Manman Xu, Yu Chen, Florent Artru. Guarantors: Yu Chen, Florent Artru.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest related to this work.

DATA AVAILABILITY STATEMENT

No data related to this publication.

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REFERENCES

1. Jalan R, Yurdaydin C, Bajaj JS, Acharya SK, Arroyo V, Lin H-C, et al. Toward an improved definition of acute-on-chronic liver failure. Gastroenterology. 2014;147(1):4–10. https://doi.org/10.1053/j.gastro.2014.05.005
2. Sarin SK, Choudhury A, Sharma MK, Maiwall R, Al Mahtab M, Rahman S, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific association for the study of the liver (APASL): an update. Hepatol Int. 2019;13(4):353–90. https://doi.org/10.1007/s12072-019-09946-3
3. Wu T, Li J, Shao L, Xin J, Jiang L, Zhou Q, et al. Development of diagnostic criteria and a prognostic score for hepatitis B virus-related acute-on-chronic liver failure. Gut. 2018;67(12):2181–91. https://doi.org/10.1136/gutjnl-2017-314641
4. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013;144(7):1426.e1–1437.e1. https://doi.org/10.1053/j.gastro.2013.02.042
5. O'Leary JG, Reddy KR, Garcia-Tsao G, Biggins SW, Wong F, Fallon MB, et al. NACSELD acute-on-chronic liver failure (NACSELD-ACLF) score predicts 30-day survival in hospitalized patients with cirrhosis. Hepatology. 2018;67(6):2367–74. https://doi.org/10.1002/hep.29773
6. Mahmud N, Kaplan DE, Taddei TH, Goldberg DS. Incidence and mortality of acute-on-chronic liver failure using two definitions in patients with compensated cirrhosis. Hepatology. 2019;69(5):2150–63. https://doi.org/10.1002/hep.30494
7. Moreau R, Gao B, Papp M, Bañares R, Kamath PS. Acute-on-chronic liver failure: a distinct clinical syndrome. J Hepatol. 2021;75(Suppl 1):S27–35. https://doi.org/10.1016/j.jhep.2020.11.047
8. Arroyo V, Moreau R, Jalan R. Acute-on-Chronic liver failure. N Engl J Med. 2020;382(22):2137–45. https://doi.org/10.1056/NEJMra1914900
9. Albillos A, Martin-Mateos R, Van der Merwe S, Wiest R, Jalan R, Álvarez-Mon M. Cirrhosis-associated immune dysfunction. Nat Rev Gastroenterol Hepatol. 2022;19(2):112–34. https://doi.org/10.1038/s41575-021-00520-7
10. López-Vicario C, Checa A, Urdangarin A, Aguilar F, Alcaraz-Quiles J, Caraceni P, et al. Targeted lipid omics reveals extensive changes in circulating lipid mediators in patients with acutely decompensated cirrhosis. J Hepatol. 2020;73(4):817–28. https://doi.org/10.1016/j.jhep.2020.03.046
11. Zaccherini G, Aguilar F, Caraceni P, Clària J, Lozano JJ, Fenaille F, et al. Assessing the role of amino acids in systemic inflammation and organ failure in patients with ACLF. J Hepatol. 2021;74(5):1117–31. https://doi.org/10.1016/j.jhep.2020.11.035
12. Graupera I, Isus L, Coll M, Pose E, Díaz A, Vallverdú J, et al. Molecular characterization of chronic liver disease dynamics: from liver fibrosis to acute-on-chronic liver failure. JHEP Rep. 2022;4(6):100482. https://doi.org/10.1016/j.jhepr.2022.100482
13. Clària J, Curto A, Moreau R, Colsch B, López-Vicario C, Lozano JJ, et al. Untargeted lipid omics uncovers lipid signatures that distinguish severe from moderate forms of acutely decompensated cirrhosis. J Hepatol. 2021;75(5):1116–27. https://doi.org/10.1016/j.jhep.2021.06.043
14. Moreau R, Clària J, Aguilar F, Fenaille F, Lozano JJ, Junot C, et al. Blood metabolomics uncovers inflammation-associated mitochondrial dysfunction as a potential mechanism underlying ACLF. J Hepatol. 2020;72(4):688–701. https://doi.org/10.1016/j.jhep.2019.11.009
15. Zhang IW, Curto A, López-Vicario C, Casulleras M, Duran-Güell M, Flores-Costa R, et al. Mitochondrial dysfunction governs immunometabolism in leukocytes of patients with acute-on-chronic liver failure. J Hepatol. 2022;76(1):93–106. https://doi.org/10.1016/j.jhep.2021.08.009
16. Clària J, Stauber RE, Coenraad MJ, Moreau R, Jalan R, Pavesi M, et al. Systemic inflammation in decompensated cirrhosis: characterization and role in acute-on-chronic liver failure. Hepatology. 2016;64(4):1249–64. https://doi.org/10.1002/hep.28740
17. Trebicka J, Amoros A, Pitarch C, Titos E, Alcaraz-Quiles J, Schierwagen R, et al. Addressing profiles of systemic inflammation across the different clinical phenotypes of acutely decompensated cirrhosis. Front Immunol. 2019;10:476. https://doi.org/10.3389/fimmu.2019.00476
18. Langer M.-M, Eickelmann C, Kleinbongard P, Lange CM. Impaired mitochondrial complex IV respiration in peripheral blood mononuclear cells discriminates acute-on-chronic liver failure from acute decompensation. J Hepatol. 2022;77(3):874–6. https://doi.org/10.1016/j.jhep.2022.04.037
19. Bernsmeier C, van der Merwe S, Périanin A. Innate immune cells in cirrhosis. J Hepatol. 2020;73(1):186–201. https://doi.org/10.1016/j.jhep.2020.03.027
20. Trovato FM, Zia R, Napoli S, Wolfer K, Huang X, Morgan PE, et al. Dysregulation of the lysophosphatidylcholine/autotaxin/lysophosphatidic acid axis in acute-on-chronic liver failure is associated with mortality and systemic inflammation by lysophosphatidic acid-dependent monocyte activation. Hepatology. 2021;74(2):907–25. https://doi.org/10.1002/hep.31738
21. Korf H, du Plessis J, van Pelt J, De Groote S, Cassiman D, Verbeke L, et al. Inhibition of glutamine synthetase in monocytes from patients with acute-on-chronic liver failure resuscitates their antibacterial and inflammatory capacity. Gut. 2019;68(10):1872–83. https://doi.org/10.1136/gutjnl-2018-316888
22. Triantafyllou E, Woollard KJ, McPhail MJW, Antoniades CG, Possamai LA. The role of monocytes and macrophages in acute and acute-on-chronic liver failure. Front Immunol. 2018;9:2948. https://doi.org/10.3389/fimmu.2018.02948
23. Gustot T, Fernandez J, Garcia E, Morando F, Caraceni P, Alessandria C, et al. Clinical Course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology. 2015;62(1):243–52. https://doi.org/10.1002/hep.27849
24. Zhang X, Ying Y, Zhou P, Liu X, Li R, Tao Y, et al. A stepwise evaluation of hepatitis B virus-related acute-on-chronic liver failure to optimize the indication for urgent liver transplantation. Dig Dis Sci. 2021;66(1):284–95. https://doi.org/10.1007/s10620-020-06149-x
25. Choudhury A, Jindal A, Maiwall R, Sharma MK, Sharma BC, Pamecha V, et al. Liver failure determines the outcome in patients of acute-on-chronic liver failure (ACLF): comparison of APASL ACLF research consortium (AARC) and CLIF-SOFA models. Hepatol Int. 2017;11(5):461–71. https://doi.org/10.1007/s12072-017-9816-z
26. Xu M.-M, Kong M, Yu P.-F, Cao Y.-Y, Liu F, Zhu B, et al. Clinical course and outcome patterns of acute-on-chronic liver failure: a multicenter

retrospective cohort study. J Clin Transl Hepatol. 2021;9(000):626–34. https://doi.org/10.14218/JCTH.2020.00179
27. Karvellas CJ, Garcia-Lopez E, Fernandez J, Saliba F, Sy E, Jalan R, et al. Dynamic prognostication in critically ill cirrhotic patients with multiorgan failure in ICUs in Europe and North America: a multicenter analysis. Crit Care Med. 2018;46(11):1783–91. https://doi.org/10.1097/CCM.0000000000003369
28. Engelmann C, Thomsen KL, Zakeri N, Sheikh M, Agarwal B, Jalan R, et al. Validation of CLIF-C ACLF score to define a threshold for futility of intensive care support for patients with acute-on-chronic liver failure. Crit Care. 2018;22(1):254. https://doi.org/10.1186/s13054-018-2156-0
29. Drolz A, Horvatits T, Rutter K, Landahl F, Roedl K, Meersseman P, et al. Lactate improves prediction of short-term mortality in critically ill patients with cirrhosis: a multinational study. Hepatology. 2019;69(1):258–69. https://doi.org/10.1002/hep.30151
30. Li F, Thuluvath PJ. EASL-CLIF criteria outperform NACSELD criteria for diagnosis and prognostication in ACLF. J Hepatol. 2021;75(5):1096–103. https://doi.org/10.1016/j.jhep.2021.05.033
31. Balcar L, Semmler G, Pomej K, Simbrunner B, Bauer D, Hartl L, et al. Patterns of acute decompensation in hospitalized patients with cirrhosis and course of acute-on-chronic liver failure. United Eur Gastroenterol J. 2021;9(4):427–37. https://doi.org/10.1002/ueg2.12089
32. Levesque E, Saliba F, Ichaï P, Samuel D. Outcome of patients with cirrhosis requiring mechanical ventilation in ICU. J Hepatol. 2014;60(3):570–8. https://doi.org/10.1016/j.jhep.2013.11.012
33. Choudhury A, Vijayaraghavan R, Maiwall R, Kumar M, Duan Z, Yu C, et al. "First week" is the crucial period for deciding living donor liver transplantation in patients with acute-on-chronic liver failure. Hepatol Int. 2021;15(6):1376–88. https://doi.org/10.1007/s12072-021-10206-6
34. Wang L, Xu W, Li X, Chen D, Zhang Y, Chen Y, et al. Long-term prognosis of patients with hepatitis B virus-related acute-on-chronic liver failure: a retrospective study. BMC Gastroenterol. 2022;22(1):162. https://doi.org/10.1186/s12876-022-02239-4
35. Lin S, Zhang K, Zhang J, Wang M, Velani B, Zhu Y. Long-term outcomes of patients with hepatitis B virus-related acute on chronic liver failure: an observational cohort study. Liver Int. 2019;39(5):854–60. https://doi.org/10.1111/liv.14072
36. Yoon EL, Kim TY, Lee CH, Kim TH, Cho HC, Lee SS, et al. Long-term prognosis of acute-on-chronic liver failure survivors. J Clin Gastroenterol. 2019;53(2):134–41. https://doi.org/10.1097/MCG.0000000000000987
37. Piano S, Tonon M, Vettore E, Stanco M, Pilutti C, Romano A, et al. Incidence, predictors and outcomes of acute-on-chronic liver failure in outpatients with cirrhosis. J Hepatol. 2017;67(6):1177–84. https://doi.org/10.1016/j.jhep.2017.07.008
38. Pompili E, Baldassarre M, Zaccherini G, Tufoni M, Iannone G, Pratelli D, et al. Low haemoglobin level predicts early hospital readmission in patients with cirrhosis and acute decompensation. JHEPReport. 2023;5:100698. https://doi.org/10.1016/j.jhepr.2023.100698
39. Trebicka J, Fernandez J, Papp M, Caraceni P, Laleman W, Gambino C, et al. The PREDICT study uncovers three clinical courses of acutely decompensated cirrhosis that have distinct pathophysiology. J Hepatol. 2020;73(4):842–54. https://doi.org/10.1016/j.jhep.2020.06.013
40. Wang T, Tan W, Wang X, Zheng X, Huang Y, Li B, et al. Role of precipitants in transition of acute decompensation to acute-on-chronic liver failure in patients with HBV-related cirrhosis. JHEP Rep. 2022;4(10):100529. https://doi.org/10.1016/j.jhepr.2022.100529
41. Zanetto A, Pelizzaro F, Campello E, Bulato C, Balcar L, Gu W, et al. Severity of systemic inflammation is the main predictor of ACLF and bleeding in patients with acutely decompensated cirrhosis. J Hepatol. 2022;S0168-8278(22):03110–5. https://doi.org/10.1016/j.jhep.2022.09.005
42. Zanetto A, Pelizzaro F, Mion MM, Bucci M, Ferrarese A, Simioni P, et al. Toward a more precise prognostic stratification in acute decompensation of cirrhosis: the Padua model 2.0. United Eur Gastroenterol J. 2023;11(9):815–24. https://doi.org/10.1002/ueg2.12472
43. Gao F-Y, Liu Y, Li X-S, Ye X-Q, Sun L, Geng M-F, et al. Score model for predicting acute-on-chronic liver failure risk in chronic hepatitis B. World J Gastroenterol. 2015;21(27):8373–81. https://doi.org/10.3748/wjg.v21.i27.8373
44. Yuan L, Zeng B-M, Liu L-L, Ren Y, Yang Y-Q, Chu J, et al. Risk factors for progression to acute-on-chronic liver failure during severe acute exacerbation of chronic hepatitis B virus infection. World J Gastroenterol. 2019;25(19):2327–37. https://doi.org/10.3748/wjg.v25.i19.2327
45. Yu M, Li X, Lu Y, Jie Y, Li X, Shi X, et al. Development and validation of a novel risk prediction model using recursive feature elimination algorithm for acute-on-chronic liver failure in chronic hepatitis B patients with severe acute exacerbation. Front Med. 2021;8:748915. https://doi.org/10.3389/fmed.2021.748915
46. Xu Y, Li Y, Li S, Xue S, Liu J. Dual-energy CT quantification of extracellular liver volume predicts short-term disease progression in patients with hepatitis B liver cirrhosis-acute decompensation. Insights Imaging. 2023;14(1):51. https://doi.org/10.1186/s13244-023-01393-x
47. Choudhury A, Kumar M, Sharma BC, Maiwall R, Pamecha V, Moreau R, et al. Systemic inflammatory response syndrome in acute-on-chronic liver failure: relevance of "golden window": a prospective study. J Gastroenterol Hepatol. 2017;32(12):1989–97. https://doi.org/10.1111/jgh.13799
48. Artru F, Samuel D. Approaches for patients with very high MELD scores. JHEP Rep. 2019;1:53–65. https://doi.org/10.1016/j.jhepr.2019.02.008
49. Morrison MA, Artru F, Trovato FM, Triantafyllou E, McPhail MJ. Potential therapies for acute-on-chronic liver failure. Liver Int. 2023. https://doi.org/10.1111/liv.15545
50. Zanetto A, Northup P, Roberts L, Senzolo M. Haemostasis in cirrhosis: understanding destabilising factors during acute decompensation. J Hepatol. 2023;78(5):1037–47. https://doi.org/10.1016/j.jhep.2023.01.010
51. Blasi A, Patel VC, Adelmeijer J, Azarian S, Hernandez Tejero M, Calvo A, et al. Mixed fibrinolytic phenotypes in decompensated cirrhosis and acute-on-chronic liver failure with hypofibrinolysis in those with complications and poor survival. Hepatology. 2020;71(4):1381–90. https://doi.org/10.1002/hep.30915
52. Campello E, Zanetto A, Bulato C, Maggiolo S, Spiezia L, Russo FP, et al. Coagulopathy is not predictive of bleeding in patients with acute decompensation of cirrhosis and acute-on-chronic liver failure. Liver Int. 2021;41(10):2455–66. https://doi.org/10.1111/liv.15001
53. Premkumar M, Saxena P, Rangegowda D, Baweja S, Mirza R, Jain P, et al. Coagulation failure is associated with bleeding events and clinical outcome during systemic inflammatory response and sepsis in acute-on-chronic liver failure: an observational cohort study. Liver Int. 2019;39(4):694–704. https://doi.org/10.1111/liv.14034
54. Bihari C, Patil A, Shasthry SM, Baweja S, Kumar G, Sarin SK. Viscoelastic test-based bleeding risk score reliably predicts coagulopathic bleeding in decompensated cirrhosis and ACLF patients. Hepatol Int. 2020;14(4):597–608. https://doi.org/10.1007/s12072-020-10036-y
55. Trebicka J, Gu W, Ibáñez-Samaniego L, Hernández-Gea V, Pitarch C, Garcia E, et al. Rebleeding and mortality risk are increased by ACLF but reduced by pre-emptive TIPS. J Hepatol. 2020;73(5):1082–91. https://doi.org/10.1016/j.jhep.2020.04.024
56. Caraceni P, Riggio O, Angeli P, Alessandria C, Neri S, Foschi FG, et al. Long-term albumin administration in decompensated cirrhosis

(ANSWER): an open-label randomised trial. Lancet. 2018;391(10138):2417–29. https://doi.org/10.1016/S0140-6736(18)30840-7
57. Larrue H, D'Amico G, Pol O, Yong L, Bucsics T, Rudler M, et al. TIPS prevents further decompensation and increases survival in cirrhotic patients with portal hypertension: an individual patient data meta-analysis. J Hepatol. 2023. https://doi.org/10.1016/j.jhep.2023.04.028
58. Berry K, Lerrigo R, Liou IW, Ioannou GN. Association between transjugular intrahepatic portosystemic shunt and survival in patients with cirrhosis. Clin Gastroenterol Hepatol. 2016;14(1):118–23. https://doi.org/10.1016/j.cgh.2015.06.042
59. Unger LW, Stork T, Bucsics T, Rasoul-Rockenschaub S, Staufer K, Trauner M, et al. The role of TIPS in the management of liver transplant candidates. United Eur Gastroenterol J. 2017;5(8):1100–7. https://doi.org/10.1177/2050640617704807
60. de Franchis R. Portal hypertension VII: proceedings of the 7th baveno consensus workshop: personalized care in portal hypertension. Springer International Publishing; 2022.
61. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018;69:406–60. https://doi.org/10.1016/j.jhep.2018.03.024
62. Piano S, Mahmud N, Caraceni P, Tonon M, Mookerjee RP. Mechanisms and treatment approaches for ACLF. Liver Int. 2023. https://doi.org/10.1111/liv.15733
63. Sersté T, Cornillie A, Njimi H, Pavesi M, Arroyo V, Putignano A, et al. The prognostic value of acute-on-chronic liver failure during the course of severe alcoholic hepatitis. J Hepatol. 2018;69(2):318–24. https://doi.org/10.1016/j.jhep.2018.02.022
64. Engelmann C, Habtesion A, Hassan M, Kerbert AJ, Hammerich L, Novelli S, et al. Combination of G-CSF and a TLR4 inhibitor reduce inflammation and promote regeneration in a mouse model of ACLF. J Hepatol. 2022;77(5):1325–38. https://doi.org/10.1016/j.jhep.2022.07.006
65. Arab JP, Sehrawat TS, Simonetto DA, Verma VK, Feng D, Tang T, et al. An open-label, dose-escalation study to assess the safety and efficacy of IL-22 agonist F-652 in patients with alcohol-associated hepatitis. Hepatology. 2020;72(2):441–53. https://doi.org/10.1002/hep.31046
66. Agarwal B, Cañizares RB, Saliba F, Ballester MP, Tomescu DR, Martin D, et al. Randomized, controlled clinical trial of the DIALIVE liver dialysis device versus standard of care in patients with acute-on- chronic liver failure. J Hepatol. 2023;0(1):79–92. https://doi.org/10.1016/j.jhep.2023.03.013
67. Artru F, Louvet A, Ruiz I, Levesque E, Labreuche J, Ursic-Bedoya J, et al. Liver transplantation in the most severely ill cirrhotic patients: a multicenter study in acute-on-chronic liver failure grade 3. J Hepatol. 2017;67(4):708–15. https://doi.org/10.1016/j.jhep.2017.06.009
68. Belli LS, Duvoux C, Artzner T, Bernal W, Conti S, Cortesi PA, et al. Liver transplantation for patients with acute-on-chronic liver failure (ACLF) in Europe: results of the ELITA/EF-CLIF collaborative study (ECLIS). J Hepatol. 2021;75(3):610–22. https://doi.org/10.1016/j.jhep.2021.03.030
69. Michard B, Artzner T, Deridder M, Besch C, Addeo P, Castelain V, et al. Pretransplant intensive care unit management and selection of grade 3 acute-on-chronic liver failure transplant candidates. Liver Transpl. 2022;28(1):17–26. https://doi.org/10.1002/lt.26280
70. Thuluvath PJ, Thuluvath AJ, Hanish S, Savva Y. Liver transplantation in patients with multiple organ failures: feasibility and outcomes. J Hepatol. 2018;69(5):1047–56. https://doi.org/10.1016/j.jhep.2018.07.007
71. Sundaram V, Patel S, Shetty K, Lindenmeyer CC, Rahimi RS, Flocco G, et al. Risk factors for posttransplantation mortality in recipients with grade 3 acute-on-chronic liver failure: analysis of a North American consortium. Liver Transpl. 2022;28(6):1078–89. https://doi.org/10.1002/lt.26408
72. Sundaram V, Jalan R, Wu T, Volk ML, Asrani SK, Klein AS, et al. Factors associated with survival of patients with severe acute-on-chronic liver failure before and after liver transplantation. Gastroenterology. 2019;156(5):1381–91.e3. https://doi.org/10.1053/j.gastro.2018.12.007
73. Artru F, Goldberg DS, Kamath PS. Priority for ACLF grade 3 patients. J Hepatol. 2023;78(6):1118–23. https://doi.org/10.1016/j.jhep.2022.12.026
74. Huebener P, Sterneck MR, Bangert K, Drolz A, Lohse AW, Kluge S, et al. Stabilisation of acute-on-chronic liver failure patients before liver transplantation predicts post-transplant survival. Aliment Pharmacol Ther. 2018;47(11):1502–10. https://doi.org/10.1111/apt.14627
75. Sundaram V, Kogachi S, Wong RJ, Karvellas CJ, Fortune BE, Mahmud N, et al. Effect of the clinical course of acute-on-chronic liver failure prior to liver transplantation on post-transplant survival. J Hepatol. 2020;72(3):481–8. https://doi.org/10.1016/j.jhep.2019.10.013
76. Dong V, Karvellas CJ. Acute-on-chronic liver failure: objective admission and support criteria in the intensive care unit. JHEP Rep. 2019;1:44–52. https://doi.org/10.1016/j.jhepr.2019.02.005
77. Philips CA, Kedarisetty CK. Palliative care for patients with end-stage liver disease. J Clin Exp Hepatol. 2023;13(2):319–28. https://doi.org/10.1016/j.jceh.2022.08.003
78. McPhail MJW, Auzinger G, Bernal W, Wendon JA. Decisions on futility in patients with cirrhosis and organ failure. Hepatology. 2016;64(3):986. https://doi.org/10.1002/hep.28539
79. Farias AQ, Curto Vilalta A, Momoyo Zitelli P, Pereira G, Goncalves LL, Torre A, et al. Genetic ancestry, race, and severity of acutely decompensated cirrhosis in Latin America. Gastroenterology. 2023;165(3):696–716. https://doi.org/10.1053/j.gastro.2023.05.033
80. Hernaez R, Kramer JR, Liu Y, Tansel A, Natarajan Y, Hussain KB, et al. Prevalence and short-term mortality of acute-on-chronic liver failure: a national cohort study from the USA. J Hepatol. 2019;70(4):639–47. https://doi.org/10.1016/j.jhep.2018.12.018
81. Griemsmann M, Tergast TL, Simon N, Kabbani A.-R, Manns MP, Wedemeyer H, et al. Nosocomial infections in female compared with male patients with decompensated liver cirrhosis. Sci Rep. 2022;12(1):3285. https://doi.org/10.1038/s41598-022-07084-9
82. Lehmann J, Praktiknjo M, Nielsen MJ, Schierwagen R, Meyer C, Thomas D, et al. Collagen type IV remodelling gender-specifically predicts mortality in decompensated cirrhosis. Liver Int. 2019;39(5):885–93. https://doi.org/10.1111/liv.14070
83. Chan KK.-S, Au K.-Y, Fung W.-C, Wong C.-Y, Chan AC.-Y, Lo RC.-L. Sex-specific analysis of microRNA profiles in HBV-associated cirrhosis by small RNA-sequencing. Hepatol Commun. 2022;6(12):3473–86. https://doi.org/10.1002/hep4.2096

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