Review

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Acute-on-chronic liver failure in patients with alcohol-related liver disease

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Summary

The spectrum of alcohol-related liver diseases (ALD) includes steatosis, steatohepatitis, progressive liver fibrosis, and cirrhosis. Acute-on-chronic liver failure (ACLF) is a recently defined entity that occurs in patients with chronic liver diseases and is characterised by acute decompensation, organ failures and a high risk of short-term mortality. Active alcohol consumption, alcoholic hepatitis and bacterial infections are the most frequent events precipitating the development of ACLF in the context of ALD (ALD-ACLF). The specific management of this entity remains unknown and the place of salvage liver transplantation controversial. This overview details the current knowledge on specific aspects of epidemiology, pathophysiology, prognosis and management of ALD-ACLF.

Keywords: Cirrhosis; Organ failure; Inflammation; Alcoholic hepatitis; Infection; Liver transplantation.

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The concept of ACLF

Acute-on-chronic liver failure (ACLF) is a recently defined entity that occurs in patients with cirrhosis and is characterised by acute deterioration, organ failures and a high risk of short-term mortality.[1,2] Currently different definitions have been created by several scientific societies (the Asian Pacific Association for the Study of the Liver [APASL], the European Association for the Study of the Liver – Chronic Liver Failure consortium [EASL-CLIF], the North American Consortium for the Study of End-Stage Liver Disease [NACSELD], reviewed in detail elsewhere.[3] The syndrome is characterised pathophysiologically by systemic inflammation and altered host response to injury. From the clinical perspective, the condition can be described using the Predisposition, Injury, Response, Organ Failure (PIRO) concept.[4] Factors such as age, aetiology of the underlying liver disease and previous decompensation constitute *P*redisposition. The event precipitating the development of ACLF in previously stable cirrhosis constitutes *I*njury. Whether ACLF is associated with infection, inflammation and/or immune failure describes *R*esponse and the type and number of organ failures constitute *O*rgan failure. In alcohol-related ACLF (ALD-ACLF), the underlying liver disease is alcohol-related cirrhosis. The following section describes the clinical features, prognosis, pathogenesis and treatment of ALD-ACLF. Finally, this article also discusses the current controversies surrounding the concept of ACLF.

The precipitating events for ALD-ACLF

Active alcohol consumption as a trigger event of ACLF

In the CANONIC European observational study, active excessive alcohol consumption (defined by more than 14 units per week in women and 21 units per week in men) within the past 3 months was recognised as the second most frequent event precipitating event ACLF (~25%) after bacterial infection.[2] Patients with acute decompensated alcoholic cirrhosis and active excessive alcohol consumption were younger and had more marked biological alterations (higher total bilirubin, leukocyte count and international normalized ratio). The prevalence and the severity of ACLF were also increased in this subgroup compared with the rest of patients, suggesting that alcohol *per se* triggered the liver damage responsible of ACLF.[2] In South Asia, alcohol consumption is currently the most frequent acute hepatic insult (~50%) responsible for ACLF.[5] Alcoholic hepatitis (AH) could be the underlying entity that induced ACLF but very few liver biopsies (proving the diagnosis) were performed in these studies. We know that AH frequently progresses to multiple organ failures, which are a leading cause of death.[6] In a prospective cohort of patients with severe AH (sAH, modified discriminant function ≥32), EASL-CLIF ACLF was reported in 65% of cases either at the time of sAH diagnosis or within a 6-month follow-up period.[6] Currently, we do not know if some alcohol-induced ACLF is a specific form of ALD or merely a clinical progression of sAH. To answer to this question, we need high-quality liver histological and molecular data correlated with well-defined clinical entities. A study of hospitalised patients with alcohol-related cirrhosis with liver biopsy suggested an association between specific histological features (ductular bilirubinostasis and cholangiolitis) and ACLF.[8] More recently, histological studies have demonstrated marked evidence of cell death due to apoptosis and necroptosis.[9,10]

Other trigger events of ACLF in patients with ALD (alcoholic cirrhosis)

Patients with ALD are prone to develop infection due to multiple defects in their innate and adap-

Key point

Globally, excessive alcohol consumption has been shown to be one of the most frequent events precipitating ACLF.

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tive immune system. This susceptibility is reviewed in detail elsewhere.[11] In Europe and North America, bacterial infections are the most identifiable precipitating factor of ACLF in patients with cirrhosis from all aetiologies, in particular alcoholic cirrhosis.[2,12] Moreover, bacterial infection is the only independent predictor of the occurrence of ACLF in a cohort of patients with sAH.[7] In China, bacterial infection is considered the precipitating event for ACLF in 44% of patients.[13] In other parts of Asia, these data are lacking because the APASL definition of ACLF requires an acute hepatic insult and bacterial infection is not considered as a part of the syndrome. Superimposed acute viral hepatitis A or E, hepatitis B flare and drug-induced liver injury are other events that can precipitate ACLF in patients with alcoholic cirrhosis. A classical diagnostic workup must be made to exclude these aetiologies.

Specific mechanisms of ALD-ACLF

Key point

The specific clinical and pathophysiologic features of ACLF are the presence of organ failure(s) and evidence of systemic and hepatic inflammation.

The specific clinical and pathophysiologic features of ACLF, irrespective of aetiology, are the presence of organ failure(s) and evidence of systemic and hepatic inflammation.[2,4] The pathogenic mechanism underlying the development of ACLF is unclear and the mechanism underlying systemic inflammation is unknown. Based upon the existing data, one can start to build a hypothesis, which is described in Fig. 1 and will be explored further in this section.

Evidence of systemic inflammation and immune dysfunction in ALD-ACLF and its association with mortality

Systemic inflammation

It is clear from many studies that systemic inflammation is a particular feature of ACLF in general and significantly over represented in ALD-ACLF.[2,4,6] Data from the CANONIC study clearly demonstrated that patients with ACLF have more marked systemic inflammatory response manifested by elevated white cell count (WCC) and C-reactive protein (CRP).[2] Indeed, the study confirmed that WCC was indeed an independent predictor of mortality and this has been incorporated into the CLIF-Consortium ACLF (CLIF-C ACLF) prognostic scoring system to define the risk of death.[14] It is not clear whether this represents an alteration of host response to injury or whether it is due to an inability to resolve inflammation as other studies suggested that a lack of reduction in CRP was associated with increased mortality.[3] It is intriguing to note that the increase in WCC is predominantly due to neutrophilia. The neutrophil/lymphocyte ratio was shown be predictive of increased mortality in an ALD-ACLF study.[15,16] The mechanism underlying this discrepant and important alteration in WCC is unclear but may be due to the effect of increased granulocyte-colony stimulating factor (G-CSF) that was observed in patients with ALD-ACLF, as G-CSF is known to act on the bone marrow to increase granulopoeisis whilst reducing the lymphocyte and monocyte lineages.[17] This hypothesis would argue for a deleterious effect of administering G-CSF to patients with ALD-ACLF but the available clinical data suggest the opposite.[18] More studies are needed to better define the mechanisms underlying alterations in the cellular phenotypes in ALD-ACLF and the role of G-CSF.

Circulating cytokines

The changes in WCC and CRP are also associated with increases in the circulating cytokines in patients with ACLF.[19–21] However, the changes in the pattern of cytokines are not consistent and depend upon the severity of ACLF, the underlying cause of the liver disease and the precipitating event. Data from a sub-study of the CANONIC study demonstrated clearly that both pro and anti-inflammatory cytokines were elevated in patients with ALD-ACLF suggesting the existence of a mixed inflammatory response.[21] IL-8 tended to be more elevated in patients when alcohol abuse was the main precipitating event, whereas IL-6 was more likely to be elevated in the patients in whom infection was the precipitating event. In the patients with no identifiable precipitating events, cytokinemia was limited, suggesting perhaps that this group of patients are pathophysiologically different.[21] The mechanisms underlying these widely varying cytokine profiles are unclear but suggest the existence of a complex alteration of the immune system. Therefore, it was not surprising to note that large studies using corticosteroids, pentoxifylline or targeting of TNFα have not been successful in patients with AH, which is an important cause of ALD-ACLF.[22–24] Studies

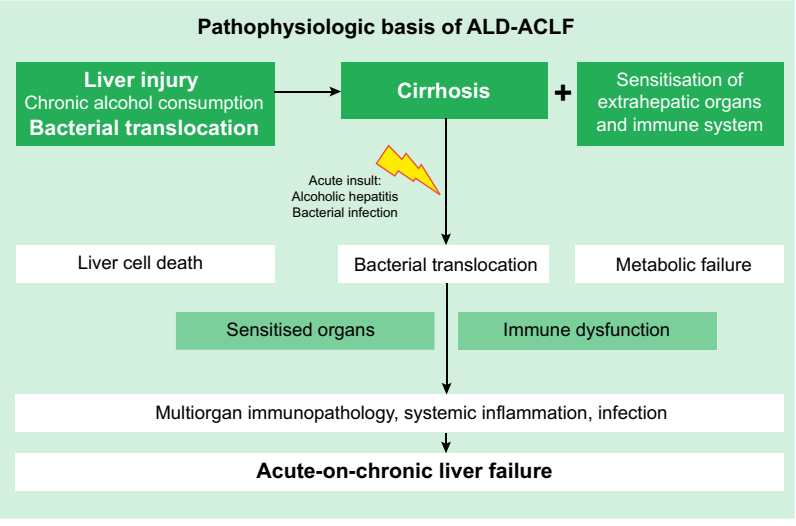

Fig. 1. Overview of the current hypothesis concerning the pathophysiology of acute-on-chronic liver failure in the context of alcohol-related liver disease. ALD-ACLF, alcohol-related acute-on-chronic liver failure.

targeting IL-1β are currently underway and the results of these studies are awaited.

Immune cell dysfunction

These changes in circulating markers of inflammation are associated with changes in the functional characteristics of the circulating inflammatory cells in ALD-ACLF. It is becoming clear that with increasing severity of ACLF, there is a shift of the immune cellular function from a pro-inflammatory to an anti-inflammatory phenotype, which may explain the very high risk of infection in these patients, which is frequently the cause of death.[2,7,22,25] All cell lineages and both innate and adaptive immune defects are observed in ALD-ACLF but the mechanisms underlying these changes are unclear. The available data are summarised (Table 1). In general, it appears that although cellular functional defects are measurable, evidenced by an inability of the cells to kill and clear bacteria, they also generate pro-inflammatory molecules and these defects are due in part to circulating humoral factors.[26–33] In *in vitro* studies, removal of endotoxin from plasma was shown to restore neutrophil function, and monocyte function could be rescued by albumin as it binds to prostaglandin E2.[26,27] Circulating ligands of PD1 and TIM3 receptor, which alter lymphocyte function have been shown to be present in ALD-ACLF.[29] Taken together, these studies point to the potential of developing targeted interventions to address cellular dysfunction and also to more general strategies such as plasma exchange and the use of extracorporeal liver assist devices such as DIALIVE, trials of which are underway.

Although it is clear that dysregulated inflammation is a key pathophysiological mechanism underlying the pathogenesis of organ failure and risk of infection, it is not clear whether it is the cause of ACLF or its effect. In future studies, it will be important to perform longitudinal studies to better define the role of dysregulated inflammation in ALD-ACLF.

Possible mechanisms underlying systemic inflammation in ALD-ACLF

Role of cell death

It has become clear that molecules released following cell death, so-called damage associated molecular patterns have immunogenic properties and can result in systemic inflammation. As ACLF is associated with hepatocyte cell death, the type and severity of cell death is important in determining their immunogenicity (Fig. 2). Although early small studies suggested that apoptosis is the predominant form of cell death in ACLF,[9] a large study using plasma samples obtained from the CANONIC study has shown incontrovertibly that the predominant mechanism of cell death in ALD-ACLF is non-apoptotic, which may provide an explanation for the severity of systemic inflammation observed.[10] Recent studies have provided evidence for the importance of hepatocyte necroptosis, which is a form of regulated necrosis that requires the proteins RIPK3 and MLKL. It is induced by interferons, death receptors, toll-like receptors, intracellular RNA and DNA sensors, and other mediators such as lipopolysaccharides.[34] In preliminary studies, necroptosis was observed to be an important mode of cell death in patients with ACLF and the inhibition of RIPK3 phosphorylation, a key regulator of necroptosis prevented the occurrence of ACLF in an animal model.[35] Pyroptosis is a lytic type of regulated necrosis which is inherently associated with severe inflammation. It is mediated by "inflammatory caspases" such as caspase 1, and caspase 5 in humans (and caspase 11 in rodents).[36] In an unbiased RNA sequence analysis in an animal model of AH, caspase 11 (CASP4 in humans) was identified. Caspase 11 and caspase 4 activation were observed in mouse models and patients with AH, respectively. Inducing caspase 11 deficiency was associated with protection of animals from AH.[37] The data suggest that hepatocyte cell death may precede systemic inflammation and may be its cause rather than its consequence.

Table 1. Cellular basis of immune dysfunction in ALD-ACLF, associated mechanisms and possible therapeutic targets. (Adapted from[11])

Cell type	Main functional derangement	Mechanism	Therapeutic target
Lymphocytes[29]	Reduced T-cell IFN production in response to LPS. Increased T-cells producing IL-10.	Increased expression of PD1 and TIM-3.	Antibodies to PDI and TIM3 restored function.
Monocytes and macrophages[27,28,30,31]	Reduced LPS induced TNF production. Reduced pro-inflammatory cytokine secretion and bacterial killing. Reduced pro-inflammatory cytokine secretion in response to LPS. Reduced monocyte oxidative burst and bacterial killing. Reduced phagocytic capacity.	Reduced DR3 expression. Increased Prostaglandin E2. Increased expression of MERTK. Reduced $gp91^{phox}$ subunit of NADPH oxidase. Metabolic reprogramming and altered cellular bioenergetics.	Reduce bacterial translocation. PGE2 receptor antagonists. COX-2 inhibitors. Albumin infusion. Inhibition of MERTK, UNC569. NADPH modulators. Glutamine synthase inhibitors.
Neutrophils[26,32,33]	Increased resting burst but reduced *E. Coli* induced oxidative burst and reduced phagocytosis. Reduced bactericidal activity.	Involvement of humoral factor possibly LPS and toll-like 4 receptors. Defect of myeloperoxidase release and the AKT/p38 MAP kinase pathway.	Bacterial translocation. Removal of LPS using plasma exchange or specific filters. TLR4 antagonists. TLR7/8 agonists.

ALD-ACLF, alcohol-related acute-on-chronic liver failure; LPS, lipopolysaccharide.

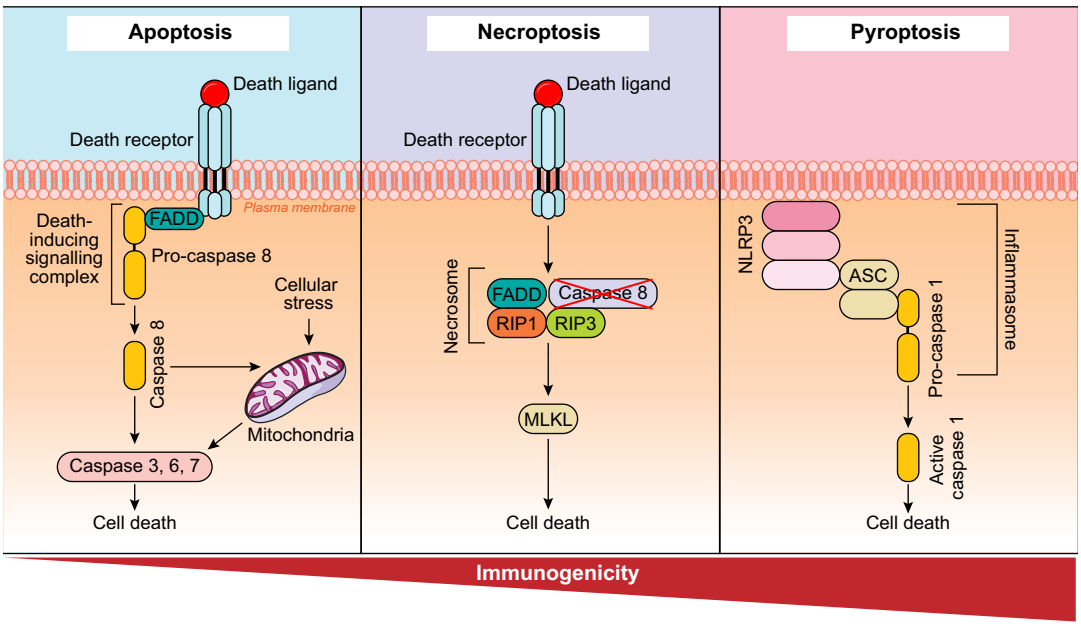

Fig. 2. Description of pathways and immunogenicity associated with 3 types of cell death (apoptosis, necroptosis and pyroptosis).

Role of bacterial translocation

Many studies have shown evidence of bacterial translocation in patients with cirrhosis and that targeting the gut with poorly absorbed antibiotics such as norfloxacin and rifaximin prevents the major cirrhosis complications such as acute kidney injury and hepatic encephalopathy.[38,39,69] The bacterial products referred to as pathogen-associated molecular patterns can activate the pathogen recognition receptors on immune cells resulting in systemic inflammation and subsequent immunopathology. The importance of this pathway in the pathogenesis of ACLF is illustrated by the fact that infection is the most common precipitating factor for its development. More recently, studies in patients with AH have clearly demonstrated that increased concentrations of circulating lipopolysaccharide are associated with a more marked systemic inflammatory response and increased risk of death.[6]

Role of changes in metabolism

Ammonia is the best-studied metabolic toxin. It is produced predominantly in the gut, in which the microbiome plays a role.[40] It has widespread pathological effects not only on the brain but also on the immune system and muscle metabolism, and has been shown to be associated with stellate cell activation and worsening portal hypertension, all features of ACLF.[41–43] More recently, studies have addressed the metabolic basis of immune dysfunction in ACLF. Studying the metabolomic signature of the plasma of patients with ACLF has revealed a marked dysfunction of the tryptophan/kyneurenin pathway, which has a key role in monocyte function although its exact role is not yet defined.[44] Metabolomic signatures based on ^{1}H NMR spectroscopy accurately discriminated between patients that died and those that survived following an episode of acute decompensation.[45] The spectra that distinguished non-survivors from survivors were attributed to reduced phosphatidylcholines and lipid resonances, with increased lactate and altered amino acid metabolism. Interestingly, the lysophosphatidyl choline levels correlated inversely with biochemical and histological markers of liver cell death. Whether these changes are a cause or effect is not clear.

Key point

A recently developed prognostic scoring system, the CLIF-C ACLF score, has significantly improved the prediction of short- and medium-term mortality compared to classical prognostic scores.

Prognosis of ACLF in patients with ALD

Prognostic tools have been developed to try and better predict outcomes of patients with ACLF. According the CANONIC study, the initial grade of ACLF, the clinical course, and a specifically designed score (CLIF-C ACLF score) seemed to accurately estimate outcomes.[2,14,46] The number of organ failures defined by the CLIF-C OF score and the presence of kidney and/or neurological dysfunction defined the grade of ACLF (see Table 2). We also observed that ACLF was an extremely dynamic syndrome associated with potential resolution, improvement, stabilisation or deterioration. Indeed, the grade of ACLF between the 3rd and 7th day after diagnosis seemed to predict outcomes more accurately than the initial grade.[46] Finally, investigators combined CLIF-OF score with age and WCC to design a specific ACLF score, the CLIF-C ACLF score (web calculator at http://www.efclif.com).[14] This score significantly improved the prediction of short and medium-term mortality compared with classical scores (model for end-stage liver disease [MELD], MELD-Na, and Child-Pugh) in patients with ACLF from the CANONIC cohort and in a validation cohort of cirrhotic

Table 2. The EASL-CLIF definition of ACLF. (Adapted from[2,14])

	The CLIF Consortium-organ failure scoring system		
Organ/system	**Subscore = 1**	**Subscore = 2**	**Subscore = 3**
Liver (total bilirubin, mg/dl)	<6	≥6–<12	**≥12**
Kidney (creatinine, mg/dl)	<2	**≥2–<3.5**	**≥3.5 or RRT**
Brain (West-Haven grade HE)	0	1–2	**3–4**
Coagulation (INR)	<2	≥2–<2.5	**≥2.5**
Circulation (MAP, mmHg)	≥70	<70	**vasopressors**
Lung			
PaO_2/FiO_2 or	>300 or	≤300–>200 or	**≤200 or**
SpO_2/FiO_2	>357	≤357–>214	**≤214**

Text in bold represents criteria used to define organ failures.
Grade of ACLF. ACLF grade 1 (ACLF-1): patients with single kidney failure; patients with non-renal organ failure plus renal dysfunction (creatinine 1.5–1.9 mg/dl) and/or brain dysfunction (grade 1–2 HE). ACLF-2: patients with 2 organ failures. ACLF-3: patients with 3 or more organ failures.
ACLF, acute-on-chronic liver failure; EASL-CLIF, European Association for the Study of the Liver – Chronic Liver Failure consortium; FiO_2, fraction of inspired oxygen; HE, hepatic encephalopathy; INR, international normalized ratio; MAP, mean arterial pressure; PaO_2, partial pressure of arterial oxygen; RRT, renal replacement therapy; SpO_2, pulse oximetric saturation.

patients admitted to the intensive care unit. The type of precipitating event, in particular active excessive alcohol consumption within the past 3 months, did not influence the mortality rates or the clinical course of ACLF.[2,46] Another score has been developed by the APASL ACLF research consortium in a large cohort of patients with APASL-defined ACLF (50% had active alcohol consumption as the precipitating event).[5] The score considers total bilirubin, grade of hepatic encephalopathy, international normalized ratio, lactate and serum creatinine (http://www.aclf.in/?page=doctor_aarc_grade_cal) and performed better than Child-Pugh score, MELD score, sequential organ failure assessment (SOFA) score, and CLIF-SOFA score in the prediction of 28-day mortality. Like the CLIF-C ACLF score, the changes in the score during the first week increase its accuracy.

The presence of ACLF and its grade makes it possible to stratify patients with sAH into prognostic groups. In a prospective cohort of patients with sAH, the 28-day cumulative incidences of death of patients without ACLF or with ACLF-1, ACLF-2 or ACLF-3 were 10%, 31%, 58% and 72% respectively.[7] In this observational study, the accuracy of CLIF-C ACLF score was relatively poor (C-index 0.68) for early identification of patients at high risk of death at 28 and 168 days. In the STOPAH trial, the area under the curve when using the CLIF-C ACLF score to determine 28-day and 90-day mortality was 0.79 and 0.77, respectively, similar to other classical AH scores measured at baseline (MELD, Glasgow alcoholic hepatitis score [GAHS], age, serum bilirubin, international normalized ratio and serum creatinine [ABIC] score).[47]

Therapeutic impact of ACLF in the treatment of patients with ALD

Treatments of sAH in the context of ACLF

Currently, corticosteroids remain the first line therapy for sAH. In a prospective cohort of consecutive unselected patients with biopsy-proven sAH, the probability of a response to corticosteroids according to the Lille model was reduced in patients with ACLF compared to those without ACLF and progressively among grades of ACLF (77% for patients without ACLF, 52% for ACLF-1, 42% for ACLF-2 and 8% for ACLF-3).[7] This critical point raises concerns about administration of corticosteroids to patients with ACLF-3. In the STOPAH trial (randomised controlled trial [RCT] assessing the efficacy of corticosteroids in patients with sAH), patients were selectively recruited and those with severe renal impairment and those with inotropic support were excluded.[22] A subanalysis of this trial confirmed the reduced probability of response to corticosteroids and higher risk of infection in patients with ACLF but, if a response to corticosteroids was achieved (observed in 37% of patients with ACLF-2 or 3), the survival benefit was maintained irrespective of ACLF grade.[47] With the current data, we cannot provide a definitive recommendation on the systematic use of corticosteroids in sAH with ACLF (in particular high grades of ACLF) or state that ACLF is an absolute contraindication. We suggest balancing risks and benefits on a case-by-case basis.

Pentoxyfilline has been suggested as an alternative treatment when corticosteroids are contraindicated but recent trials and a meta-analysis concluded that pentoxyfilline administration alone or in combination with corticosteroids is unable to improve short-term survival in patients with sAH.[22,48] Moreover, pentoxyfilline is also ineffective in non-responders to corticosteroids.[49] Currently, pentoxyfilline has not been assessed specifically in patients with sAH and ACLF.

Potential specific treatments of ACLF

Based on the hypothesis that released endogenous substances contribute to propagation of liver dysfunction and extrahepatic organ failures, detoxification devices have been assessed. Albumin dialysis (molecular adsorbent recirculating system, MARS®) improved liver biochemistry, renal and cerebral functions and attenuated hyperdynamic circulations in alcohol-related ACLF.[50,51] In RCTs, devices (MARS® and fractionated plasma separation and adsorption system, Prometheus®)

did not demonstrate a survival benefit for patients with ACLF (the majority of patients having alcoholic cirrhosis and/or alcohol as a precipitating event).[52,53] These trials were designed before establishment of a validated definition of ACLF.

G-CSF has recently been proposed as a potential treatment for ACLF. G-CSF promotes mobilisation of bone marrow stem cells and proliferation of hepatic progenitor cells in patients with AH.[54] G-CSF is also able to increase circulating and intrahepatic myeloid and plasmacytoid dendritic cells and T lymphocytes in patients with ACLF.[55] Some small RCTs have observed a reduction of infectious episodes, improvement of liver function and also significant survival benefit compared with standard medical treatment in patients with APASL ACLF.[18,56,57] Nevertheless, additional randomised trials are needed to confirm these observations before establishing recommendations.

Some pilot studies suggest that healthy donor faecal microbiota transplantation has a beneficial effect on the outcome of patients with alcohol-related ACLF.[58,59] A retrospective uncontrolled study on 23 patients with sAH and ACLF not eligible for corticosteroids and not undergoing liver transplantation (LT) but receiving salvage faecal microbiota transplantation showed promising survival rates of 73% for patients with ACLF-1 and 58% for ACLF-2 or 3 at 548 days.[59] Unfortunately, it is not currently possible to make a clear recommendation about this emerging therapy, as high-quality trials are lacking.

Liver transplantation for ACLF in the context of patients with ALD

Because of poor short-term outcomes, the option of LT for patients with ACLF is frequently considered but highly controversial. We can state that LT in sicker patients is unquestionably associated with substantial survival benefit but could impact the survival of other potential recipients on the waiting list and result in less acceptable longer term results after LT.[60] Experiences with LT in selected patients with ACLF or multiple organ failures (including ACLF-3 patients) were associated with acceptable 1-year post-LT survival (from 75 to 84%).[46,61,62] In expert centres, results of living-donor LT are reported as equivalent to deceased-donor LT for patients with ACLF.[63,64] However, some publications reported significantly lower post-LT survival rates for patients with ACLF-3.[65,66] Currently, the question of objective limits, beyond which the patient is considered too sick to be transplanted and LT is considered futile, remains unanswered. Another major issue regarding LT in ACLF is the timing. Indeed, early LT is preferred to avoid clinical deterioration, impacting the post-LT results, but the potential recovery or improvement observed in ACLF after critical management has been suggested to maximise the chance of LT success. Some authors proposed prioritising patients with ACLF on the waiting list after an initial stabilisation.[67]

Active alcohol consumption and sAH are frequently the factors that precipitate alcohol-related ACLF. The controversial 6-month rule of alcohol abstinence and the acceptable rates of alcohol relapse published in a report on LT for highly selected patients are reviewed in detail in another article of this *Special Issue*. Particularly, patients with ACLF are frequently in very poor clinical condition (severe hepatic encephalopathy, unstable status) and have a short clinical window, making precise assessments about the type of alcohol consumption, social network, and familial support very challenging. We need to prospectively validate a fast-track multidisciplinary protocol to assess these different aspects and guarantee acceptable alcohol relapse rates after LT in the context of ACLF.

Key point

LT in sicker patients is associated with substantial survival benefit but could impact the survival of other potential recipients on the waiting list with better long-term survival prospects.

Controversies

The term "acute-on-chronic liver failure" (ACLF) designates a condition where acute liver injury is superimposed upon chronic liver disease with or without cirrhosis. One perspective is that the main organ dysfunction in ACLF is liver injury and organ failures are secondary to that. However, data from the CANONIC study suggests that nearly 50% of patients have renal failure as the presenting organ failure in ALD-ACLF.[2] Sepsis is widely recognised as the main precipitating event of ACLF.[2] Some investigators argue that sepsis is secondary to liver injury and should not be considered a precipitating event. Again, the data from the NACSELD consortium and CLIF group have shown that sepsis is one of the most important precipitating events.[2,25,68] There is also a suggestion that there should be an element of reversibility such that reversal to baseline hepatic function can potentially occur with or without liver support. Therefore, it was suggested that the term ACLF should not be applied to patients with decompensated cirrhosis. This assertion is not supported by the studies of the CLIF consortium who show that the short-term outcome of patients with ACLF, with or without previous decompensation, is similar, which indicates a degree of reversibility even for previously decompensated patients.[46]

A uniform definition of ACLF that can be applied world-wide is required. The current variability in definitions makes it appear that ACLF is a different disease depending on which continent the patient lives in. The variability in the definitions as well as the criteria for organ failure have been compared in a recent publication.[3] Current disagreements between definitions of different societies are because the so-called "defining"

criteria like organ failure are, in fact, "prognostic" criteria. Since ACLF can progress to multiple organ failures, liver specific scoring systems such as the Child-Pugh or MELD scores are unlikely to be optimal. Inflammation is likely an early critical event and therefore markers such as WCC, CRP, or procalcitonin may be helpful as early prognostic tests that herald the onset of extrahepatic failure. Once extrahepatic organ failures set in, organ failure specific scores like the CLIF-OF score are prognostic.

Conclusions

In conclusion, the occurrence of ACLF in patients with ALD who present with acute deterioration changes their prognosis and identifies a distinct subset of patients with an extremely high risk of short-term mortality. These patients have a distinct pathophysiology characterised by intense systemic inflammation, immune failure and high risk of infection. The prognosis of these patients with ALD-ACLF is defined by the number of organ failures. Current therapies, such as steroids, are likely to be ineffective and associated with increased risk of infection for those with AH in association with ACLF. Liver transplantation saves the lives of patients with ALD-ACLF, but future studies are needed to better define selection criteria.

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Conflicts of interest

TG gives advices to Promethera Biosciences and Martin Pharmaceuticals. RJ has ongoing research collaboration with Yaqrit and Takeda Pharmaceutical Company Ltd. RJ is also inventor of a drug, L-ornithine phenylacetate (OCR-002), which University College London has licensed to Ocera Therapeutics. RJ is also the founder of University College London spin-off companies Yaqrit Ltd. And CYBERLIVER Ltd.

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

Authors' contributions

TG designed the manuscript. TG and RJ wrote the manuscript. TG and RJ prepared the final version. We thank Patrick Kamath for his contribution to the 'controversies' section.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.12.008.

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Author names in bold designate shared co-first authorship

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