ALCOHOL AND ACUTE ON CHRONIC LIVER FAILURE

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Funding: none.

Conflict of interest: MPB and RS declare no conflict of interest. Rajiv Jalan has research collaborations with Yaqrit and Takeda. Rajiv Jalan is the inventor of OPA which has been patented by University College London and licensed to Mallinckrodt Pharma. He is also a founder of Yaqrit limited, a spin-out company from University College London. He has also co-founded Hepyx Ltd. and Cyberliver Ltd.

Electronic word count: 2928.

Number of figures and tables: 4 Tables, 1 Figure.

Abstract:

Acute-on-chronic liver failure (ACLF) is a clinical syndrome that occurs in patients with cirrhosis characterised by acute deterioration, organ failure and high short-term mortality. Alcohol is one of the leading causes of ACLF and the most frequently reported aetiology of underlying chronic liver disease. Among patients with alcoholic hepatitis (AH), ACLF is a frequent and severe complication. It is characterized by both immune dysfunction associated to an increased risk of infection and high grade systemic inflammation that ultimately induce organ failure. Diagnosis and severity of ACLF determines AH prognosis, and therefore, ACLF prognostic scores should be used in severe AH with organ failure. Corticosteroids remain the first-line treatment for severe AH but it seems insufficient when ACLF is associated. Novel therapeutic targets to contain the excessive inflammatory response and reduce infection have been identified and are under investigation. With liver transplantation remaining as one of the most effective therapies for severe AH and ACLF, adequate organ allocation represents a growing challenge. Hence, a clear understanding of the pathophysiology, clinical implications and management strategies of ACLF in AH is essential for hepatologist, which is narrated briefly in this review.

Keywords: Acute-On-Chronic Liver Failure, Alcoholic Hepatitis, Cirrhosis.

Abbreviations: Acute-on-chronic liver failure (ACLF), alanine aminotransferase (ALT), alcoholic hepatitis (AH), Asian Pacific Association for the Study of the Liver (APASL), aspartate aminotransferase (AST), damage-associated molecular patterns (DAMPs), European Association for the Study of the Liver - Chronic Liver Failure Consortium (EASL-CLIF), Glasgow alcoholic hepatitis score (GAHS), international normalized ratio (INR), interleukin (IL), model for end-stage liver disease (MELD), N-acetylcysteine (NAC), North American Consortium for the Study of End-Stage Liver Disease (NACSELD), pathogen-associated molecular patterns (PAMPs), tumour necrosis factor (TNF), World Gastroenterology Organization (WGO)

Introduction

Acute-on-chronic liver failure (ACLF) is a clinical syndrome that occurs in patients with cirrhosis characterised by acute deterioration and organ failure[1]. Although heterogenous definitions of this syndrome have been created by different societies, the end point of each of them is its high short-term mortality[1-9]. Alcohol is one of the leading causes of ACLF and the most frequently reported aetiology of underlying chronic liver disease[10-11]. Nevertheless, whether acute alcoholic hepatitis (AH) with organ failure is a different entity or a subtype of ACLF is up for debate. In this review we discuss health care burden, pathophysiology, prognosis and available as well as novel therapeutic options for alcohol-related-ACLF based on the latest developments in this rapidly evolving entity.

Operating definitions of ACLF and AH

As a means of identifying patients at high risk of mortality, the Asian Pacific Association for the Study of the Liver (APASL) created its first definition of ACLF in 2009[12] based on expert opinion and provided updated versions in 2014 and 2019[13-14]. The North American Consortium for the Study of End-Stage Liver Disease (NACSELD) then conducted two prospective studies, including only cirrhosis patients with bacterial infections and both infected and non-infected cirrhosis patients, respectively[15-16]. Finally, in 2013 the European Association for the Study of the Liver - Chronic Liver Failure Consortium (EASL-CLIF) performed the largest prospective study (CLIF-ACLF CANONIC study) including 1343 consecutive patients admitted to the hospital for acutely decompensated cirrhosis[17]. In this study, the diagnosis of organ failures was based on a modified Sequential Organ Failure Assessment score (EASL-CLIF Consortium organ failure scoring system)[18]. Subsequently, the European criteria were extensively validated outside of Europe[19-21]. Despite an established differentiation between ACLF and acute liver failure or decompensated cirrhosis, both of which only describe an aspect of ACLF, the existing definitions still deviate from each other in several aspects such as underlying liver disease, precipitating events, presenting features, definition of organ failure and duration of the acute event (Table 1). Nevertheless, alcohol intake has been considered by all societies as an underlying aetiology and identified as a potential intrahepatic precipitating factor for the development of ACLF. To reach a uniform consensus, the World Gastroenterology Organization (WGO) proposed to define ACLF as the acute deterioration (jaundice and prolongation of the international normalized ratio -INR-) of an underlying chronic liver disease (with or without cirrhosis) leading to multiple organ failure with a high mortality risk[1].

AH is a clinical syndrome characterised by recent onset of jaundice in patients with ongoing alcohol abuse or who have ceased alcohol consumption up to several weeks before the onset of symptoms. Jaundice is often associated with other signs of liver decompensation (i.e. ascites and/or hepatic encephalopathy), fever, malaise, weight loss and malnutrition (Table 1). However, the clinical features of this syndrome can also result from sepsis, viral hepatitis or drug induced liver injury, among others. Clinical suspicion is supported by typical laboratory findings, including hyperbilirubinemia (>5 mg/dL), neutrophilia, serum levels of aspartate aminotransferase (AST) greater than twice the upper limit of normal, although usually <300 IU/ml, with an AST/alanine aminotransferase (ALT) ratio >1.5[22]. Underlying histological condition is steatohepatitis, defined by steatosis, hepatocyte ballooning and polymorphonuclear infiltrate[23]. Considering the risks of a liver biopsy, it is only indicated when there is diagnostic uncertainty to rule out other causes and can be useful for prognostication[24]. Thus, in the absence of a liver biopsy, clinical and laboratory criteria should be applied more stringently to avoid misdiagnosing AH[25]. Severe forms of AH frequently associate prolonged prothrombin time, hypoalbuminemia and decreased platelet count as well as extrahepatic organ failure in up to 48-65% of cases[26-27]. Hence, despite not all severe AH develop ACLF and not all ACLF is caused by AH, operating definitions of both entities cannot be completely separated and must be understood as an overlapping entities. Development of new models or novel markers that can predict the difference between the two entities could help in managing these patients.

Health care burden of AH in ACLF

The recognition of ACLF with all clinical implications as a new entity has expanded its burden in the last decades. The prevalence of ACLF depends on the definition used. However, it has increased world-wide, and it currently occurs in up to 35% of hospitalized patients with decompensated cirrhosis[12-21]. The increasing allocation of resources towards this syndrome has been associated with a successful reduction in mortality[28], albeit worldwide 90-day mortality remains as high as 55-61% according to a recent systematic review and meta-analysis based on the EASL-CLIF definition[10]. Alcohol is reported to be the underlying aetiology in 41-60% of patients with cirrhosis admitted for acute decompensation, representing the most common cause of chronic liver disease worldwide[10]. Globally, bacterial infection is the most frequent trigger of ACLF followed by gastrointestinal bleeding and alcohol, with alcohol as the main precipitating event in East Asia and North America[10]. The importance of AH in ACLF is also demonstrated

in the main ACLF studies as AH accounts for a large proportion of patients. AH was found to be the major non-infectious cause of acute deterioration in the studies using the APASL criteria and the precipitating event in 45% and 24% of the NACSELD and the CANONIC cohorts, respectively[14,16,17]. However, at present, it is not clear what proportion of patients with severe AH have ACLF.

Pathophysiologic basis of AH-ACLF and non-AH-ACLF

Despite a better comprehension of the pathophysiology of ACLF, many features are under investigation. Patients with ACLF are characterized by high grade systemic inflammation, manifested by elevated white cell count and C-reactive protein, as indicated by the CANONIC study[17]. In addition, other studies have shown that blood levels of cytokines such as interleukin (IL)-6, IL-8 or tumour necrosis factor (TNF)-α are also higher in patients with ACLF compared to individuals without, which correlates with the extent of organ failure and the short-term mortality[26,29-30]. AH itself represents a condition associated with systemic inflammation and organ failures[17,26]. On the other hand, it has been well described that the progression of cirrhosis correlates with an increased susceptibility to bacterial infection due to cirrhosis-associated immune dysfunction[31]. Similarly, infection is one of the main complications of severe AH, as well as one of the major causes of mortality in this setting[32-33]. This supports the widely accepted hypothesis that precipitating event/s (heavy alcohol intake with or without bacterial infection among others) lead to systemic inflammation which, in chronic liver disease patients with an altered immune system, causes organ failure in both AH-ACLF and non-AH-ACLF (Table 2, Figure 1).

Trigger event – systemic inflammation

The mechanism leading to systemic inflammation depends on the trigger factor. While bacterial infection (extrahepatic precipitant) induces a systemic inflammatory response through the recognition of pathogen-associated molecular patterns (PAMPs), AH (hepatic precipitant) produces systemic inflammation mainly through the release of damage-associated molecular patterns (DAMPs) from cell death; both PAMPs and DAMPs recognised by pattern-recognition receptors of the innate immune system, notably TLR4[3]. Moreover, hepatocyte death seems to be mediated by more immunogenic forms such as necroptosis and pyroptosis rather than apoptosis in AH-ACLF, which may provide an explanation for its severity[34-36]. In addition, chronic alcohol exposure causes intestinal dysbiosis and gut barrier dysfunction with increased bacterial translocation and higher serum concentrations of circulating lipopolysaccharide (LPS), correlating

with the severity of hepatic injury[37]. Given that infection and bacterial translocation are common in AH, inflammation not only results from DAMPs but also from PAMPs in AH-ACLF[38-39]. In response to the binding of these molecular patterns to TLR4, intracellular, proinflammatory signalling cascades are activated, leading to an upregulation of nuclear factor kappa-light-chain-enhancer of activated B cells, interferon regulatory factor and subsequently to the production of cytokines[40-41].

Altered immune response

In response to severe liver injury, circulating pluripotent bone-marrow derived stem cells are recruited that can fuse with pre-existing hepatocytes and differentiate into epithelial and hepatic stellate cells to support liver regeneration as well as provide pro-regenerative cytokines and growth factors. Furthermore, these stem cells exert anti-inflammatory functions by reducing the number of Ly6C-low CD8+ T cells, natural killer cells, and IgM+IgD+ B cells while increasing the number of immunosuppressive monocyte-derived macrophages[42-43]. Persistent immune cell stimulation from PAMPs and DAMPs "exhausts" the immune response, which switches from a predominantly iinflammatory response in patients with compensated cirrhosis to an immunodeficient stage in patients with decompensated cirrhosis and organ failure (ACLF)[31]. This seems to be the underlying mechanism also in patients with AH who develop ACLF, since their immune system is characterized by defects in both innate and adaptive immune cells[11]. Similarly, serum albumin undergoes quantitative and functional abnormalities as liver disease progresses, endangering its non-oncotic properties as an antioxidant and immunomodulator, which could also influence the patient's immune response[44-45].

Organ failure driven by inflammation

The abrupt exacerbation of systemic inflammation and the pro-oxidant environment observed in AH-ACLF and non-AH-ACLF induces several changes that ultimately induces organ failure. First, an increased stimulation of nitric oxide production induces activation of homeostatic endogenous vasoconstrictors resulting in renal vasoconstriction and hypoperfusion, renal fluid retention that accumulates in the form of ascites, dilutional hyponatraemia and hepatorenal syndrome[46-47]. Second, tissue damage both immune-mediated and from impaired tissue oxygenation and, third, mitochondrial dysfunction with reduced ATP production also contribute to organ failure[48-49]. Nonetheless, once ACLF has developed, the mechanism by which some patients will worsen, and others will improve is a crucial question that still has no answer.

Prognosis of AH is dependent on the diagnosis and severity of ACLF

As one of the fundamental principles of ACLF syndrome, patients with acutely decompensated cirrhosis can be stratified into prognostic grades (no ACLF and ACLF 1, 2 and 3) according to the number of organ failures at diagnosis. Similarly, prognosis of severe AH is dependent on ACLF grades as it was shown in a prospective cohort of 165 patients with biopsy-proven AH. As a result, 28-day cumulative incidence of death is 10%, 31%, 58% and 71% in patients with severe AH without ACLF or with ACLF-1, ACLF-2 or ACLF-3, respectively[27] (Table 1). These numbers are very similar to patients with non-AH ACLF[3]. Based on organ failures, inflammatory markers, and other parameters such as age, different prognostic scores assessing 28-day mortality have been developed (Table 3), improving the prediction of short-term mortality compared with classical scores such as model for end-stage liver disease (MELD), MELD-Na or Child-Pugh[18,50-51]. Nevertheless, none of these scores have proved a prognostic value higher than 0.8 probably due to the complexity of the entity and the influence of other factors not considered in these prognostic models. Among patients with AH-ACLF, not only an increase in white cell count but also neutrophil/lymphocyte ratio predicts mortality[52-53]. On the other hand, having an additional precipitating event such as infection also impacts outcomes negatively[17,54].

In the setting of AH, different prognostic models have also been developed aiming to identify patients at high risk of early death. The Maddrey discriminant function was the first one and remains the most widely used. It includes bilirubin and PT/INR at baseline (Table 3) with a cut-off value of 32 that identifies patients with severe AH who may benefit from specific therapy[55]. More recently, several prognostic scores such as the Glasgow alcoholic hepatitis score (GAHS; age, serum bilirubin, urea, PT and peripheral blood white cell count) and the ABIC (age, bilirubin, INR and serum creatinine) have been developed[56-57]. However, none of these scores consider failure of organs other than kidney and may underestimate the risk of death in patients with AH-ACLF; therefore, better models need to be developed. Given that no differences in mortality are reported between bacterial infections or AH as the precipitating events[17,54], applying ACLF prognostic scores to patients with severe AH who develop organ failure can be helpful in defining prognosis.

Moreover, ACLF is a dynamic disorder with a variable course in which a patient presenting with ACLF-1 to 3 can resolve, improve or worsen within a few days. Consequently, prognosis for patients with each grade of ACLF, including AH-ACLF, is more accurate when estimated 3 to 7 days after diagnosis than at baseline[58-59]. Response to therapy may also be a hallmark in prognosticating ACLF. In the setting of AH, patients classified as non-responders to corticosteroids by the Lille score are at increased risk of developing ACLF[60-61]. Therefore, progression to ACLF in AH and its futility may be determined, at least in part, by response to therapy. Currently, organs are allocated based on the MELD score. However, with only three organ systems represented in the scoring system (kidney, liver and coagulation) included in this score, prognosis of about 30-40% of patients with ACLF 3-4 can also be underestimated while on the waiting list[62]. With new evidence emerging, there is an increasing need of re-evaluating prioritization criteria on the transplant waiting list as well as developing new therapies for patients with ACLF.

Implication of a diagnosis of ACLF for the treatment of AH: current and novel therapies

The pillars of ACLF therapy consists of treating the precipitating event and provide multiorgan support. With infections as one of the most common precipitants for the development of ACLF, broad-spectrum antibiotics should be started promptly after diagnosis. The recommendation of administering empirical antifungal therapy is limited to patients with infections other than pneumonia who develop septic shock and have well-known risk factors for invasive fungal infections. Antibiotic or fungal therapy should be adjusted according to the organism isolated as soon as possible[3]. Their benefits are further supported by studies showing the positive effect of poorly absorbable rifaximin and norfloxacin in preventing cirrhosis related complications in the form of kidney injury and hepatic encephalopathy[63-64]. Extracorporeal liver support in the form of plasma exchange (APACHE; NCT03702920) and strategies targeting albumin exchange and endotoxin removal (DIALIVE; NCT03065699) are currently being studied after trials on albumin dialysis (MARS) and extracorporeal cellular therapy (ELAD) failed to improved short-term survival, compared to standard medical therapy[65-67] .

Despite its role as first-line treatment, corticosteroids exhibit a wide heterogeneity in its efficacy of improving survival rates in severe AH[68]. From 6-randomized clinical trials assessing the impact of corticosteroids on survival after 28-days, only two[69-70] showed significantly improved survival rates while four provided no evidence of benefit probably due to lack of adequate patient stratification[71-74]. Response

to corticosteroids negatively correlates with the number of organ failures at baseline (77% without ACLF, 52% with ACLF-1, 42% with ACLF-2, and 8% for ACLF-3)[27]. At the same time, infection is one of the factors that potentially limit the efficacy of corticosteroids. An ongoing study is evaluating the effect of adding the antibiotic amoxicillin-clavulanic acid to prednisolone to reduce the rate of infection in AH and potentially improve survival rates (NCT02281929). Antioxidant therapy is of theoretical interest in the treatment of AH. Because N-acetylcysteine (NAC) limits oxidative stress it has been studied in several trials of severe AH. However, NAC did not increase survival compared to standard medical therapy[75-76]. A multicentre French trial compared the effects of the combination of NAC and prednisolone with significantly lower mortality, hepatorenal syndrome and infections[77]. Therefore, combination of these two therapies should be tested in a future large clinical trial.

Possible immunogenic modulator of systemic inflammation in the context of ACLF include the selective inhibition of TLR4 by TAK-242[78]. Despite proven efficacy in rodent acute liver failure and ACLF models, it failed to suppress cytokine production and improve outcomes in human trials with severely septic patients[79]. A current phase 2a trial will assess the efficacy and safety of TAK-242 in patients with AH-ACLF (NCT04620148) in response to the systemic inflammatory reaction.

While therapies targeting cytokines like TNF-α to reduce inflammation have to date not been effective in treating acute AH[80], treatment with recombinant IL-22 promises a therapeutic anti-inflammatory effect[81-82]. Interestingly, this study, which is being planned in patients with AH is likely to use ACLF classification for stratification. Another therapy exploring means of improving the regenerative capacity of the liver in patients with AH-ACLF is the treatment with granulocyte colony stimulating factor (G-CSF). However, results from small trials were positive but larger multicentre European studies have not shown survival benefit[83-85]. Inhibition of TLR4 combined with G-CSF application is a novel combinatorial approach that improves mortality, tissue injury, and reduces cytokine levels in animal models of ACLF[86].

Aside from treating the excessive systemic inflammatory response, modulation of the gut-liver axis by transplantation of healthy donor faecal microbiota offers an additional therapeutic approach in AH-ACLF[11,87]. With promising results in small steroid-ineligible patient samples, improving survival rates up to 548 days after administration as well as an ongoing trial comparing microbiota transplantation to steroid

therapy (NCT03091010) in severe AH, microbiota transplantation might in the future prove to be an effective treatment[88].

Regarding liver transplantation, the 1-year survival rate after surgery among patients with ACLF including ACLF-3 patients is 75%-84%, which although lower than those without ACLF, demonstrates clear transplant-benefit[89-90]. Early liver transplantation has been demonstrated to improve survival in selected patients with a first episode of severe AH not responding to medical treatment[91-92]. Additionally, adherence to the 6-month of abstinence rule is not associated with superior survival or relapse-free survival among selected patients, suggesting that selection criteria based on type of alcohol consumption, social network, familial support, response to medical treatment and posttransplant outcomes should be considered[93-94] (Table 4).

CONCLUSIONS

ACLF is a frequent and severe complication of AH characterized by immune dysfunction, severe inflammation, and an increased risk of infection, associated with short-term mortality and a great burden on health care services. ACLF grade determines AH prognosis, and therefore, ACLF prognostic scores can be a useful tool in AH. With current therapies, mainly corticosteroids, appearing to be insufficient in AH-ACLF, novel therapeutic targets have been identified and are under investigation. Some aspects such as identification of new prognostic factors, their inclusion in risk scores, improvement in selection and stratification of patients in clinical trials and development of biomarkers of response to therapy should be further explored.

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Acknowledgments:

MPB has a Rio-Hortega contract from Instituto de Salud Carlos III (CM19/00011).

Tables:

- Table 1. Definitions for acute on chronic liver failure and alcoholic hepatitis.
- Table 2. Pathophysiologic basis of acute on chronic liver failure and alcoholic hepatitis.
- Table 3. Parameters included in different prognostic scores assessing 28 day mortality in patients with acute on chronic liver failure and alcoholic hepatitis.
- Table 4. Current and novel therapies in severe alcoholic hepatitis and acute on chronic liver failure.

Figures:

- Figure 1: Pathophysiological mechanism of alcoholic hepatitis acute on chronic liver failure. Abbreviations: pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), nitric oxygen (NO).