Acute-on-chronic liver failure

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ABSTRACT

Acute-on-chronic liver failure (ACLF) is a recently recognised and defined syndrome seen in patients with liver cirrhosis and carries a high short-term mortality in excess of 15% at 28 days. ACLF is defined by organ failures (OFs) and is distinct from simple 'acute decompensation' (AD) of cirrhosis. OFs involve the liver, kidney, brain, coagulation, respiratory system and the circulation, and are defined by the European Association for the Study of the Liver Chronic Liver Failure Consortium (CLIF-C) OF score. The central pathophysiological mechanism in the development of ACLF is intense systemic inflammation, which distinguishes this syndrome from AD. The most frequent precipitating event of ACLF in the western world is bacterial infection and active alcohol intake, whereas hepatitis B flare followed by sepsis and active alcohol intake are the common precipitating events in the east. In about 40% patients with ACLF, however, no precipitating event is found. The course of ACLF is dynamic and reversible, so early identification and early initiation of supportive therapy is of utmost importance. Unfortunately, to date, there is no known specific therapy for ACLF except for liver transplantation, so the treatment revolves around institution of early organ support. Most of the patients will have a clear prognosis between 3–7 days of hospitalisation. CLIF-C ACLF score is the best available prognostic score in patients with ACLF.

Introduction

Acute decompensation (AD) of liver cirrhosis and acute-on-chronic liver failure (ACLF) are the two most important, yet pathophysiologically distinct, clinical entities seen in patients admitted to hospital with a complication of cirrhosis. Acute decompensation refers to the development of ascites, hepatic encephalopathy, gastrointestinal haemorrhage, or any combination of these conditions in patients with liver cirrhosis.[1,2] ACLF, on the other hand, is a distinct clinical condition characterised by hepatic or extrahepatic organ failures and carries high short-term mortality in excess of 15% at 28 days.[1,2] Three major features characterise this syndrome: ACLF occurs in the context of intense systemic inflammation; ACLF frequently develops in close temporal relationship with pro-inflammatory precipitating events (eg infections or alcoholic hepatitis); and ACLF is associated with single- or multiple-organ failure.

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Defining ACLF

Although there is considerable heterogeneity in the definition of ACLF primarily emanating from disagreements over the stage of underlying liver disease (from non-cirrhotic chronic liver disease to decompensated cirrhosis) and whether the precipitating event is primarily hepatic or extra-hepatic, most definitions address the role of both hepatic and extra-hepatic precipitating events and include extra-hepatic organ failures (Table 1).[1–3] The European definition, proposed by the European Association for the Study of the Liver – Chronic Liver Failure (EASL-CLIF) Consortium, applies to patients with acute decompensation of cirrhosis, with or without prior decompensating events and *does not* exclude extrahepatic precipitating events.[1] The EASL-CLIF definition

Key points

Acute-on-chronic liver failure (ACLF) is clinically and pathophysiologically distinct syndrome which carries high short-term mortality.

The diagnosis of ACLF is made in patients with acute decompensation of liver cirrhosis with organ failure. Organ failure is defined by the Chronic Liver Failure – Sequential Organ Failure Assessment (CLIF-SOFA) score which is a modification of the SOFA score.

The prognosis of patients with ACLF is better defined by CLIF-C ACLF score as compared to Child–Pugh–Turcotte and Model for End-stage Liver Disease scores.

The mainstay of the management of patients with ACLF is organ support and treatment of the precipitating event.

Patients with ACLF have comparable survival as compared to patients without ACLF post-liver transplant.

KEYWORDS: Acute-on-chronic liver failure, liver cirrhosis, organ failure, acute decompensation, high short-term mortality

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Table 1. Variations in worldwide definitions of acute-on-chronic liver failure

Consortium	EASL-CLIF[1]	APASL[2]	NACSELD[3]
Diagnostic parameters	Specified criteria using CLIF-OF score(s) for OF, 28-day mortality rate >15% from AD of cirrhosis, with/without prior decompensation often caused by infection	Acute jaundice and coagulopathy, followed by ascites ±HE <4 weeks in undiagnosed or diagnosed chronic liver disease, including cirrhosis	Specified criteria for ≥2 OFs in patients with infection, at or during admission
Exclusion criteria	Patients admitted electively for procedures or therapy, or those with hepatocellular carcinoma outside Milan criteria, or receiving immunosuppressive therapy, with HIV or with severe chronic extrahepatic disease	Bacterial infection or previous AD	Outpatients with infection, any patient with HIV infection, prior organ transplants or disseminated malignancies

AD = acute decompensation; ACLF = acute-on-chronic liver failure; APASL = Asian Pacific Association for the Study of the Liver; CLIF-OF = Chronic Liver Failure – Organ Failure; EASL-CLIF = European Association for the Study of the Liver – Chronic Liver Failure; HE = hepatic encephalopathy; NACSELD = North American Consortium for the Study of End-stage Liver Disease.

is based on the prospective investigation of 1,343 consecutive patients hospitalised for acute decompensation. The organ failures were identified by the modified Sequential Organ Failure Assessment (SOFA) score (Fig 1), which considers the function of the liver, kidney, brain, coagulation, circulation and respiration allowing stratification of patients in subgroups with different risks of death (Fig 2). The EASL-CLIF definition is validated in large-scale studies from Europe, Asia and the USA in different precipitating events.[1,4–7]

Pathophysiology of ACLF

Although the pathophysiology of ACLF is currently largely unknown, intense systemic inflammation and oxidative stress are believed to play a central and definitive role in the pathogenesis of ACLF, which distinguishes it from patients who have acute decompensation without organ failure.[8] Furthermore, the extent of systemic inflammation co-relates directly with the severity of ACLF; the higher the grade of ACLF, greater the systemic inflammation.[8]

Organ system	1 point	2 points	3 points
Liver	Bilirubin <103 µmol/L (<6.0 mg/dL)	Bilirubin 103–203 µmol/L (6.0–11.9 mg/dL)	Bilirubin ≥204 µmol/L (≥12.0 mg/dL)
Kidney	Creatinine <134 µmol/L (<1.5 mg/dL) Creatinine 134–168 µmol/L (1.5–1.9 mg/dL)	Creatinine 177–308 µmol/L (2.0–3.4 mg/dL)	Creatinine ≥309 µmol/L (≥3.5 mg/dL) or RRT
Brain (West Haven score)	Grade 0	Grade 1–2	Grade 3–4
Coagulation	INR <2.0	INR 2.0–2.4	INR ≥2.5
Circulatory	MAP ≥70 mmHg	MAP <70 mmHg	Vasopressor requirement
Respiratory	PaO_2/FiO_2 >300 SpO_2/FiO_2 >357	PaO_2/FiO_2 201–300 SpO_2/FiO_2 215–357	PaO_2/FiO_2 ≤200 SpO_2/FiO_2 ≤214

Fig 1. Diagnostic criteria of organ dysfunction and failure. Adapted from Moreau R, Jalan R, Gines P *et al*. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013;144:1426–37. FiO_2 = fraction of inspired oxygen; INR = international normalised ratio; MAP = mean arterial pressure; PaO_2 = partial pressure of oxygen; RRT = renal replacement therapy; SpO2 = oxygen saturation.

Group	Prevalence over 1,287 patients, %	28-day mortality, %	Assigned category
Absence of OF	68.3	4.4	Absence of ACLF
Single non-kidney OF without KD or BD	9.9	6.3	
Single KF	6.7	18.6	ACLF-1 (a)
Single non-kidney OF with KD or BD	4.2	27.8	ACLF-1 (b)
Two OFs	7.5	32.0	ACLF-2
Three OFs	1.9	68.0	ACLF-3 (a)
Four to six OFs	1.4	88.9	ACLF-3 (b)

Fig 2. Diagnostic criteria of acute-on-chronic liver failure and their grades. Adapted from Moreau R, Jalan R, Gines P *et al*. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013;144:1426–37. ACLF = acute-on-chronic liver failure; BD = brain dysfunction; KD = kidney dysfunction; KF = kidney failure; OF = organ failure.

Recognizing ACLF: The clinical features

ACLF occurs simultaneously or very early after the acute decompensation episode. In the CANONIC study, ACLF was present in 22.6% of patients at admission and another 8.3% of patients developed ACLF during the first 2 weeks of admission.[1] It is of utmost importance to recognise ACLF early and institute therapy to reverse the natural history of the disease, bacterial infection and alcoholic hepatitis are the most common precipitating events.[1]

The PIRO concept (predisposition, injury, response and organ involvement) helps in the early recognition of ACLF. In this example, a patient with a history of alcohol-related cirrhosis presents with fever and ascites. Laboratory investigation shows white cell count (WCC) of 16,000 /mm^3 and C-reactive protein (CRP) of 59 mg/L, ascitic fluid WCC of 800 /mm^3, serum total bilirubin of 318 µmol/L and prothrombin time of 35 seconds. In this patient, the predisposition is alcohol-related cirrhosis; injury is spontaneous bacterial peritonitis; response is systemic inflammation characterised by high WCC and CRP and the organs involved are liver and coagulation.

Although ACLF carries a high 28-day mortality of 32%, it has a highly variable course.[1] In the prospective CANONIC study, it was found that ACLF grade 1 is potentially reversible in the majority of patients: 54.5% of patients had a reversal to no ACLF, 21% remained in ACLF grade 1 and the rest (24.5%) progressed to a higher grade of ACLF to grade 2 or 3. For patients presenting with ACLF grade 3, 32% of patients had a regression in ACLF grade while the rest (68%) remained in ACLF grade 3. Thus, ACLF as a syndrome is potentially reversible in some patients.[9]

Assessment of prognosis in patients with ACLF and acute decompensation

Traditionally, the prognostic assessment of patients with liver cirrhosis has been carried out by determining the severity of portal hypertension and by assessing the severity of liver disease as defined by Childs–Pugh–Turcotte (CTP) or Model for End-stage Liver Disease (MELD) score. These scores and criteria, however, fail to correctly and adequately prognosticate patients with ACLF.[10] A new scoring system developed by the EASL-CLIF Consortium, the CLIF-C ACLF score, has superior performance in prediction of mortality in patients with ACLF. The CLIF-C ACLF score, which can be calculated via a free online calculator (www.efclif.com/scientific-activity/score-calculators/clif-c-aclf) is based on the CLIF-C organ failure score, age and white cell count, since these three factors are the independent predictors of mortality in patients with ACLF.[1] This score was obtained from CANONIC study and has been further validated in external cohorts.[11] The CLIF-C ACLF score outperforms CTP, MELD and MELD-Na scores in predicting 28-day mortality.[11]

Treatment of patients with ACLF

There is currently no specific therapy for ACLF. The main principles of treatment are to diagnose and treat precipitating events and provide supportive therapy. Organ support in an intensive care unit, with care overseen by physicians who are experts in liver disease management, may be of benefit for patients with life-threatening, single- or multiple-organ failure who have not responded to standard therapy.

Treating the precipitating event

Bacterial or fungal infection

The prevalence of infection, either precipitating or complicating, in patients with ACLF is over 50% and increases with the grade of ACLF.[12] Although the causative organisms are most often bacteria, fungal infection is not uncommon. Anti-microbial treatment should commence as soon as possible based on suspected site involved, culture/isolation results, and local anti-microbial sensitivity patterns.

Variceal haemorrhage

An episode of variceal haemorrhage should be managed according to the updated society guidance (Baveno/EASL/American Association for the Study of Liver Diseases). The standard medical treatment includes volume restitution, a combination of safe vasoconstrictor agent (somatostatin, octreotide or terlipressin), antibiotic prophylaxis and endoscopic therapy preferably within 12 hours of presentation. Additionally, a patient presenting with haematemesis should be electively intubated. Two recently published studies show that the presence of ACLF is the single most important determinant of death in patients with variceal bleeding, and pre-emptive transjugular intrahepatic portosystemic shunt (TIPSS) as well as rescue TIPSS improves survival in patients with ACLF.[13,14]

Alcoholic hepatitis

Although prednisolone therapy is indicated in patients with alcoholic hepatitis, the response to prednisolone is negatively correlated with the number of organ failures at baseline.[15] The added susceptibility of patients with ACLF to new infection makes it even more challenging to use steroids in these patients. A careful assessment for ongoing infection is of utmost importance in decision making for steroid therapy. The response to steroids should be assessed on day 7 with the Lille score, and if there is no response on day 7, the treatment should be discontinued.

Acute viral hepatitis or reactivation

There is no specific agent for acute viral hepatitis except for hepatitis B. In the event of hepatitis B virus infection at presentation, potent nucleotide or nucleoside analogues should be started at the earliest pending the confirmation based on viral deoxyribonucleic acid load.[2]

Supportive therapy

Cardiovascular and renal support

In the western world, acute kidney injury is the most common organ failure.[1] Withdrawal of diuretics, volume expansion with intravenous albumin, as well as urine tests to identify whether the acute renal injury is acute tubular necrosis or type 1 hepato-renal syndrome should be undertaken.[16] If there is no response to volume expansion and withdrawal of diuretics, treatment with vasoconstrictor agents should be started. The likelihood of renal response to vasoconstriction is inversely related to the number of organ failures.[17] norepinephrine is the first-line vasopressor in the management of persistent shock.

Treatment of encephalopathy

The airway should be protected with elective intubation in patients with high-grade encephalopathy (grade 3/4). Lactulose therapy and concomitant use of rifaximin can lead to rapid resolution of hepatic encephalopathy; care should be taken not to induce profuse diarrhoea. Albumin dialysis can be used in patients with grade 3 or 4 hepatic encephalopathy refractory to lactulose treatment.

Extracorporeal liver support

Thus far, randomised clinical trials of extra-corporeal liver support devices have failed to show any mortality benefit in patients with

ACLF. These include the albumin dialysis and an extracorporeal liver device incorporating hepatocytes compared with standard medical therapy.[18,19]

Liver transplantation

Liver transplantation is currently the only known and efficacious treatment for patients with ACLF. The 1-year survival rates after liver transplantation among patients with ACLF with one or two organ failures do not differ significantly from patients without organ failures. In patients with three or more organ failures, the survival post-transplantation approaches 80% as compared with survival rates of less than 20% among patients who do not undergo liver transplantation.[10,20]

Conclusion

ACLF has emerged to be the most common cause of inpatient death in cirrhosis, and is a major public health problem in view of the increasing rate of liver disease mortality in the UK and globally. ACLF is characterised by marked systemic inflammation and organ failure(s), usually associated with a precipitating event. The development of validated scoring systems sets the foundation for assessment of prognosis and stratifying patients for clinic. ■

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