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REVIEW

Acute-on-chronic liver failure: to admit to intensive care or not?

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Abstract

Acute-on-chronic liver failure is used to describe an acute decline in liver function in a patient with existing liver disease combined with other organ failure. Acute-on-chronic liver failure is associated with high short-term mortality, and the greater the number and severity of organ failures, the higher the mortality. The most commonly identified precipitants of acute-on-chronic liver failure include bacterial infection, gastrointestinal haemorrhage, viral hepatitis and recent excessive alcohol intake. Since some of these aetiologies are treatable, organ failure may return to pre-decompensation levels in up to 55% of patients. As a result, a trial of critical care treatment may be appropriate for many of these patients. Clinical scoring tools may help clinicians recognise futility, allowing timely withdrawal of organ support and shifting the focus of care toward palliation.

Key words: Acute-on-chronic liver failure; Acute decompensation of cirrhosis; Intensive care

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Introduction

Chronic liver disease, characterised by jaundice, coagulopathy and encephalopathy and sustained over at least a 6-month period, develops as a result of progressive destruction of the liver parenchyma. The liver's ability to regenerate in the face of chronic hepatotoxic insults results in fibrosis and cirrhosis.

Liver transplantation offers a realistic treatment for patients with severe and deteriorating chronic liver disease, but acute decompensation is the main cause of hospitalisation in patients with cirrhotic liver disease (Kim et al, 2016). The limitation of donated organs means that in the UK and other countries, 10% of patients on the waiting list for transplantation die (Jalan and Williams, 2002; Kim et al, 2006; Neuberger, 2016; Husen et al, 2019). Supporting patients through acute decompensation episodes, in the intensive care unit if necessary, may offer them the chance to survive to transplantation.

Patients living with chronic liver disease often face a slow deterioration in liver function with intermittent bouts of acute decompensation. Acute-on-chronic liver failure, first described in 2002 (Jalan and Williams, 2002), occurs in a subset of patients where an acute deterioration in liver function is associated with multiorgan failure and has a very high short-term mortality (Jalan and Williams, 2002; Olson and Kamath, 2011; Jalan et al, 2012). This similarity to acute decompensation is confusing to clinicians (Arroyo et al, 2020) and, as the definition depends so much on the prognosis, the inability to predict the outcome means that clinicians are often reluctant to admit patients to intensive care.

In 2013, the World Congress of Gastroenterology published a consensus definition of acute-on-chronic liver failure (Wlodzimirow et al, 2013) based on statements from the Asian Pacific Association for Study of the Liver and the European and American Associations for Study of the Liver (Sarin et al, 2009, 2014; Olson and Kamath, 2011). Acute-on-chronic liver failure is now widely accepted as 'a syndrome in patients with chronic liver disease characterised by acute hepatic decompensation, resulting in liver failure and extrahepatic organ failure(s) that is associated with increased mortality' (Jalan et al, 2014).

A potential concern with this definition of acute-on-chronic liver failure is that it depends on the clinician anticipating a patient's increased mortality within the following 28 days. From the point of view of the intensivist, the diagnosis of and differentiation between acute decompensation and acute-on-chronic liver failure can be distracting when faced with a patient in need of organ support. This review outlines the causes of acute-on-chronic liver failure,

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discusses ways of assessing the likelihood of survival on the intensive care unit and suggests strategies to ensure that patients for whom death is inevitable do not suffer a prolonged stay on the intensive care unit. While admitting all patients with acute decompensation to the intensive care unit would be one possible action, this may impose prolonged, uncomfortable and eventually futile treatment. Instead, the focus of the intensivist should be on whether the patient's organ failures could be improved to a stage where they may be discharged from intensive care and ultimately from hospital. It may then be possible to assess the patient for transplantation. Although the path is long, patients who have reversibility in their acute disease may derive a benefit from critical care and admission should be considered. Similarly, patients who do not respond to treatment and in whom mortality is inevitable should not undergo prolonged futile treatment.

The CANONIC study and CLIF-SOFA

The European Association for the Study of the Liver – Chronic Liver Failure consortium conducted the landmark study that better defined acute-on-chronic liver failure in European patients. The Chronic Liver Failure Acute-on Chronic Liver Failure in Cirrhosis (CANONIC) study described a condition characterised by the presence of organ failure and a high short-term mortality rate (Moreau et al, 2013). They studied 1343 patients admitted to 29 European transplant centres with decompensation of cirrhotic liver disease. Patients were divided into groups according to the severity of presentation graded from no acute-on-chronic liver failure to ACLF3, according to the pattern, degree and number of failing organs and associated mortality rates (Table 1).

They found that acute-on-chronic liver failure is a common condition, with a prevalence of 30% in patients with decompensated liver disease. Acute-on-chronic liver failure was more common in a younger population, with a mean patient age of 56 years (Moreau et al, 2013). Unsurprisingly, the CANONIC study described increased mortality rates associated with increasing severity and the number of organ dysfunctions.

A large retrospective 10-year study from North America (Hernaez et al, 2019) studied 72 316 patients with acute decompensation. They used the acute-on-chronic liver failure criteria identified in the CANONIC study and had very similar findings: a prevalence rate of 26% and overall mortality rates of 25.5% and 40% at 28 and 90 days respectively. A post-hoc analysis of 507 patients with cirrhosis in the USA and Canadian NACSELD (The North American Consortium for the Study of End Stage Liver Disease) database (Bajaj et al, 2014) found 30-day mortalities in patients with two, three and four organ failures of 48.7%, 64% and 77% respectively. Furthermore, a study documenting outcomes in Chinese patients with hepatitis B also reported mortalities of 23.2%, 60.5% and 93.1% for ACLF 1, 2 and 3 (Wu et al, 2018).

Table 1. Grades of acute-on-chronic liver failure (ACLF), definition and associated mortality

ACLF grade	Definition	28-day mortality	90-day mortality
No ACLF	1. No organ failure 2. Single non-kidney organ failure but creatinine <132 µmol/litre and no hepatic encephalopathy grade 3/4 3. Patients with hepatic encephalopathy grade 3/4 and creatinine <132 µmol/litre	4.7%	14%
ACLF 1	1. Single organ kidney failure 2. Single organ failure of liver, coagulation circulation or respiration with hepatic encephalopathy 1/2 and/or creatinine 133–167 µmol/litre 3. Hepatic encephalopathy 3/4 and creatinine 133–167 µmol/litre	22.1%	40.7%
ACLF 2	Any two organ failures	32.0%	52.3%
ACLF 3	Any three or more organ failures	76.7%	79.1%

From Moreau et al (2013)

In summary, acute-on-chronic liver failure occurs in 26–30% of patients with acute decompensation and mortality correlates with the number of organs failing. Around half of all patients improve, and even in those with three or more organ failures (ACLF 3), approximately 15% improve to a state of no organ failure within 28 days, while with ACLF 2 and 1 this can be higher, at 35% and 55% respectively (Gustot et al, 2015).

Management of acute-on-chronic liver failure

The decision to admit for supportive care in the intensive care unit is predicated on being able to intervene in the precipitating event. In the CANONIC and North American cohort study, the majority of patients had an identifiable cause, including bacterial infection, gastrointestinal haemorrhage and active alcoholism within the past 3 months (Moreau et al, 2013; Hernaez et al, 2019). This contrasts with Asia, where viral hepatitis and bacterial infection predominate as the main precipitant (Shi et al, 2015) (Table 2).

Factors that may result in acute liver failure could also precipitate acute-on-chronic liver failure. In addition, there may be an extrahepatic cause of acute-on-chronic liver failure, such as sepsis or ischaemic hepatitis. Assessment and investigation of patients with acute-on-chronic liver failure should be broad (Table 3).

There are currently no therapies that shorten acute decompensation or acute-on-chronic liver failure. Intensive care management is focused on supportive therapies and the treatment

Table 2. Commonly defined causes of acute-on-chronic liver failure

Cause	Study		
	CANONIC – Europe (Moreau et al, 2013) *n*=303 (%)	**China (Shi et al, 2015) *n*=405 (%)**	**North America (Hernaez et al, 2019) *n*=19 082 (%)**
Exacerbation of hepatitis B	–	145 (35.8)	–
Bacterial infection	98 (32.6)	113 (27.9)	2762 (14.5)
Gastrointestinal haemorrhage	40 (13.2)	40 (9.8)	1632 (8.55)
Recent active alcoholism	69 (24.5)	25 (6.1)	5469 (28.7)
Other (transhepatic intravenous porto-systemic shunt, surgery, large volume paracentesis without albumin, hepatitis, alcoholic hepatitis)	25 (8.6)	9 (2)	–
Not identifiable	126 (43.6)	83 (20.4)	–
More than one	39 (13.5)	36 (8.9)	–

Table 3. Investigating the cause of acute-on-chronic liver failure

Investigation	Precipitant	Possible treatment
History	Excessive alcohol intake	Avoidance of alcohol; steroids
	Drug-induced liver injury	Removal of precipitant; specific antidotes such as N-acetyl cysteine
Blood, urine, stool and sputum cultures Chest radiograph Ascitic tap	Bacterial infection	Broad spectrum antibiotics
Viral hepatitis screen	Hepatitis virus A, B, C, E, herpes simplex virus, herpes zoster virus, cytomegalovirus, Epstein–Barr virus, parvovirus	Specific antivirals or nucleoside or nucleotide analogues
Liver ultrasound scan Doppler Computed tomography of the abdomen	Patency of portal vein, hepatic artery and hepatic vein	Usually supportive management; possibly anticoagulation

of underlying precipitants. This is beyond the scope of this review and outlined in detail elsewhere (Arroyo et al, 2020) but, briefly, meticulous attention to cardiovascular and blood pressure management is vital. The incidence of acute kidney injury is high but often reversible, and does not necessarily mean that the patient has hepato-renal syndrome. Patients should receive adequate nutrition and supplementation of thiamine and other vitamins should be considered. N-acetyl cysteine (O'Grady et al, 1989; Harrison et al, 1990) is frequently administered even if paracetamol is not necessarily implicated in the decompensation.

There have been clinical trials of extracorporeal devices (Thompson et al, 2018), fractionated plasma separation and adsorption (Kribben et al, 2012) and albumin dialysis (Banares et al, 2013) but none improved survival compared with supportive therapy alone. Steroid therapy is recommended by some experts where decompensation is caused by alcoholic hepatitis (Lucey et al, 2009), but the risk of further immunosuppression and increased infection means that steroids should be stopped if there is no clinical response (Choi and Runyon, 2012).

Recognising futility

Alongside detecting patients with potential for improvement, it is also crucial to identify individuals who are unlikely to respond to organ support on intensive care unit. The CANONIC database was used to derive the CLIF C ACLF score. This is the sequential organ failure score modified for chronic liver disease (CLIF OF score). The CLIF C ACLF incorporates age and white cell count; both factors which had a strong influence on survival in the CANONIC study. The CLIF C ACLF score has better discriminatory power at predicting mortality in acute-on-chronic liver failure compared to other scoring systems such as the Model for End-Stage Liver Disease (MELD) (Kamath et al, 2001) and Child–Turcotte–Pugh classification of liver disease (Child and Turcotte, 1964). The CLIF C ACLF score between days 3 and 7 predicts 28-day mortality with reasonable accuracy (area under receiver operating characteristic of 0.8) and has been validated in a UK cohort (Engelmann et al, 2018). A CLIF C ACLF score ≥70 following 48 hours of organ support has been suggested as a marker of futility as at day 3 of intensive care unit care, no patients with a CLIF C ACLF score above 70 survived, despite organ support on critical care. Moreover, in a post-hoc analysis of the CANONIC data (Gustot et al, 2015), acute-on-chronic liver failure resolved or improved in 49.2%, had a steady or fluctuating course in 30.4%, and worsened in 20.4% of patients. A rising CLIF C ACLF score was associated with increased mortality at 28 days.

Taken together, these findings suggest that there is a significant cohort of patients that will respond to treatment for acute-on-chronic liver failure and may subsequently be eligible for transplantation. One strategy may be to admit a patient to the intensive care unit for limited organ support, as it is possible to identify a good proportion of patients who will not do well early in intensive care treatment. Currently, in all but extreme cases, it is impossible to identify which patients will do well from the outset. This approach is in line with intensive care treatment for many other conditions, such as exacerbations of chronic obstructive pulmonary disease or neutropaenic septic shock, where mortality is high and where a limited trial of therapy is undertaken with plans for a ceiling of supportive care or withdrawal is made for those who do not respond.

Patients with end stage liver disease have a high symptom burden and have complex palliative care needs (Low et al, 2017). Recognising the futility of ongoing critical care and meeting these palliative care needs in a critical care environment is an appropriate use of resources.

Conclusions

Acute-on-chronic liver failure is characterised by an acute deterioration of liver function in patients with underlying liver disease, associated with multi-organ failure and a high short-term mortality (40–50%). It occurs in around one third of patients with acute decompensation, where approximately half of cases are attributable to bacterial infection,

Key points

- Acute-on-chronic liver failure is an acute decompensation in a patient with chronic liver disease, characterised by worsening of jaundice, ascites and encephalopathy, with additional extrahepatic organ failure. It has a high short-term mortality (40–50%).
- Acute-on-chronic liver failure can occur as a first presentation; in these circumstances, distinguishing between acute-on-chronic liver failure and decompensation caused by irreversible decline in liver function is difficult.
- Acute-on-chronic liver failure is caused by a precipitant; bacterial infection, gastrointestinal haemorrhage, viral hepatitis and recent excessive alcohol intake are the most identified worldwide, but there is geographical variation.
- Organ failure in acute-on-chronic liver failure is potentially reversible and a trial of critical care therapy for patients with acute-on-chronic liver failure should be considered.
- Clinical scoring tools may help clinicians decide who may benefit from critical care admission but survival prediction remains imprecise.

gastrointestinal haemorrhage or recent excessive alcohol intake. Acute-on-chronic liver failure can occur in patients with early cirrhosis and treating acute-on-chronic liver failure may allow a restoration of baseline cirrhotic function, to enable the patient to be considered for liver transplantation. There are validated tools (CLIF C ACLF score) to identify patients with a poor prognosis early in their critical care admission, allowing appropriate and timely palliation without excessive treatment burden. A trial of critical care for patients with acute-on-chronic liver failure, with early withdrawal of care in patients who do not respond to medical treatment, is a reasonable approach.

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Conflict of interests

The authors declare no conflicts of interest.

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