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Acute-on-chronic liver failure

KEYWORDS

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Introduction

Acute-on-chronic liver failure (ACLF) is a recently recognized syndrome characterized by acute decompensation (AD) of cirrhosis and organ/system failure(s) (organ failure: liver, kidney, brain, coagulation, circulation and/or respiration) and extremely poor survival (28-day mortality rate 30-40%). The development of ACLF occurs in the setting of a systemic inflammation, the severity of which correlates with the number of organ failures and mortality. Systemic inflammation may cause ACLF through complex mechanisms including an exaggerated inflammatory response and systemic oxidative stress to pathogen - or danger/damage-associated molecular patterns (immunopathology) and/or alteration of tissue homeostasis to inflammation caused either by the pathogen itself or through a dysfunction of tissue tolerance.[1]

Cirrhosis in in ACLF[1]

Cirrhosis has long been recognized by the development of acute deterioration of liver and/or renal function, hepatic encephalopathy and high risk of hospital mortality in association to a precipitating event, commonly an infection. The first project of EASL-Chronic Liver Failure (CLIF) Consortium was to perform a prospective observational investigation (CANONIC Study) in a large series of patients with cirrhosis (1343 cases).

Components of the sequential Organ Failure Assessment (SOFA) score (liver, renal, cerebral, coagulation, circulatory and respiratory function) do not take into account specific features of cirrhosis, the SOFA scale was modified establishing a new scale called the CLIF-SOFA score (CLIF-SOFAs) adapted for liver patients. A simplified CLIF-SOFA score (CLIF Consortium Organ Failure score, CLIF-C OFs) with identical diagnostic criteria for organ failure and similar prognosis was later designed as shown in Figure 1.

Organ system	Score = 1	Score = 2	Score = 3
Liver, bilirubin (mg/dl)	<6	6-≤12	>12
Kidney, creatinine (mg/dl)	<2	2-<3.5	≥3.5 or renal replacement
Brain, grade (West-Haven)	0	1-2	3-4
Coagulation, INR	<2.0	2.0-<2.5	≥2.5
Circulation, MAP (mmHg)	≥70	<70	Vasopressors
Respiratory PaO_2/FiO_2	>300	≤300 and >200	≤200
or SpO_2/FiO_2	>357	>214 and ≤357	≤214

Figure1: CLIF Consortium Organ Failure Score.

The highlighted area in light blue reflects the definition of each organ/system failure. MAP, mean arterial pressure; FiO2, fraction of inspired oxygen; PaO2, partial pressure of arterial oxygen; SpO2, pulse oximetric saturation. Kidney dysfunction: serum creatinine 1.5– 1.9 mg/dl.

Relatively high "short-term mortality rate" was defined as a mortality rate equal or greater than 15% within a period of 28 days. This figure represents approximately 50% of the short-term mortality rate associated with severe sepsis in the general population. The inclusion of a short-term mortality rate threshold in the definition of ACLF was considered important because it has major therapeutic implications. Figure 2 shows that mortality rate in the CANONIC patients was clearly related to the presence and number of organ failures as defined by the CLIF-SOFA score or by the CLIF-C Ofs.

Number and types of organ failures	No kidney dysfunction and no mild-to-moderate hepatic encephalopathy	Kidney dysfunction and/or mild-to-moderate hepatic encephalopathy
No organ failure	20/562 (3.6)	19/312 (6.2)
Single liver failure	4/68 (5.9)	10/33 (30.3)
Single cerebral failure	2/25 (8.0)	1/5 (20.0)
Single coagulation failure	1/19 (5.3)	2/9 (22.2)
Single circulation or single lung failure	1/15 (6.7)	2/7 (28.6)
Single kidney failure	9/57 (15.8)	7/29 (24.1)
Two organ failures	19/66 (28.8)	12/31 (38.7)
Three organ failures or more	25/59 (86.2)	8/13 (61.5)

Figure 2: 28-day mortality in patients included in the CANONIC Study classified according to the number of organ failures and the presence or absence of kidney dysfunction and/or grade I–II hepatic encephalopathy. The highlighted area in light blue shows the subgroups of patients defined as having ACLF (with organ failure(s) and a 28-day mortality rate >15%). In brackets: % of 28-day mortality.

Role for an excessive inflammatory response in the development of organ failures in cirrhosis[1]

In patients with spontaneous bacterial peritonitis (SBP) higher levels of proinflammatory cytokines in the plasma and ascitic fluid are associated with an increased risk of renal failure .The degree of the ex vivo LPS induction of proinflammatory genes in PBMCs from patients with decompensated cirrhosis is related to prognosis: the higher the gene induction the higher the risk of short-term death. ACLF is the main cause of death in patients with cirrhosis. Together these findings suggest that patients with cirrhosis who have innate immune cells with super-inducible proinflammatory genes are at risk of developing ACLF.

Acute event in ACLF

The ACLF can develop from one or more clearly defined acute hepatic insults, which can be due to hepatotropic or nonhepatotropic agents/causes. Major etiologic agents responsible for precipitating ACLF are as follows:

1. Hepatotropic viral infections

- Among these, reactivation of Hepatitis B virus (HBV) infection and superinfection with HEV are the major causes of acute insult in ACLF

  Among the non-infectious causes, active alcohol consumption

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(within the last 28 days) remains the commonest cause
- Drug induced liver injury, consumption of complimentary and alternative medicines (CAM), severe autoimmune hepatitis, and flare of Wilson's disease are other causes of acute insult in ACLF

2. Non-hepatotropic insults like surgery, trauma, and viral infections if producing direct hepatic insult could lead to ACLF

3. Variceal bleed per se may not qualify as an acute insult for ACLF, and we need more data to ascertain this

4. In a proportion of patients, the acute hepatic insult may not be identifiable by the current routine assessment

Sepsis in ACLF[2]

Sepsis is the syndrome of the systemic inflammatory response of the host to infection. The systemic inflammatory response syndrome (SIRS) is defined by the presence of at least two of the following criteria:

(1) Altered temperature
(2) Elevated respiratory rate or hyperventilation
(3) Tachycardia
(4) Altered white blood cell count (high, low, or immature forms)

Sepsis is the most common cause of mortality in most intensive care units (ICUs). Patients with sepsis often have a striking presentation with high spiking fevers, shock, and respiratory failure. Hence, the prevailing theory of sepsis for many years was that it represented an uncontrolled inflammatory response. However, the results of more than 30 trials of diverse anticytokine and anti-inflammatory drugs showed no benefit or even reduced survival rates.

Hepatic encephalopathy in ACLF[2]

The presence of hepatic encephalopathy (HE) within 4 weeks is part of the criteria for defining acuteonchronic liver failure (ACLF). In the recent AARC data, hepatic encephalopathy was seen to be present in about 40 % of the patients. Multiple prospective and retrospective studies had shown that hepatic encephalopathy in ACLF patients is associated with higher mortality, especially in those with grades 3–4 encephalopathy.

- The HE is present in about 40–50 % of the ACLF patients
- Grades 3–4 HE in patients with ACLF is associated with increased mortality
- The MRI/CT brain may help in ACLF with Grades 3–4 HE when cerebral edema or intracerebral hemorrhage or other brain pathology is suspected
- Lactulose, rifaximin, NH_3 lowering strategies remain the main therapy for HE in patients with cirrhosis

PATHOPHYSIOLOGY OF ORGANS FAILURE[3]

- ***Pulmonary failure:***

Bacterial respiratory tract infections in cirrhotic patients represent 14% to 48% of all bacterial infections. These patients are at increased risk of pneumonia due to unprotected airway from altered consciousness, increased intra-abdominal pressure from ascites, endoscopic procedures for gastrointestinal bleeding and increased risk of bacterial translocation because of excessive use of proton pump inhibitors

- ***Haematological failure:***

Failure in the coagulation system is defined in CLIFSOFA as an international normalized ratio (INR) of 2.5 or more, or a platelet count < 20000/ML. Patients with liver disease are in a state of "rebalanced haemostasis" which results in an increase of both pro-thrombotic and anti-thrombotic factors. The most significant haematological abnormalities described in ACLF are defective platelet function and increased fibrinolysis

- ***Neurological failure:***

HE is a common manifestation of ACLF. Neurological failure is defined by CLIF-SOFA by the development of encephalopathy grade III or IV. Local and systemic disturbances have been implicated in the development of this syndrome. Patients with HE show a functional derangement in the blood brain barrier leading to increased transport of neutral amino acids and reduced transport of basic amino acids. Elevated brain ammonia level and cerebral hemodynamic dysfunction are known to be the major etiological factors. Patients with HE associated with ACLF has an extremely poor survival rate, because of a generalized inflammatory reaction that may play a role in brain and other organs dysfunction

- ***Circulatory failure***

According to the CLIF-SOFA, patients requiring inotropic drugs are considered to present circulatory failure. In ACLF there is often incapacity to appropriately increase the cardiac output in response to the insult. This finding is in contrast to decompensated cirrhosis, where cardiac output remains elevated, until advanced stages of liver disease, secondary to splanchnic vasodilatation. This cardiovascular abnormality is associated with an increased risk of death, particularly in those patients who present with renal dysfunction

- ***Kidney dysfunction***

Renal failure is defined by the CLIF-SOFA as a creatinine ≥ 2 mg/d and the use of renal replacement therapy. In the CANONIC study kidney failure was the most frequent OF for ACLF grades (55.8%), followed by liver, cerebral, and coagulation failures (43.6%, 27.7% and 24.1%, respectively). Undoubtedly, systemic haemodynamics and cardiac dysfunction play an important role in the development of renal failure

- ***Liver failure***

Liver failure is defined by the CLIF-SOFA as a total bilirubin ≥ 12 mg/dL. The hallmark of the liver manifestation of ACLF is hyperbilirubinemia and coagulopathy. Liver inflammation has a capital importance on increased portal pressure. Mechanisms proposed are changes in vascular smooth muscle cells, activation of hepatic stellate cells, reduced nitric oxide activity secondary to endothelial dysfunction and upregulation of sympathetic tone

Treatment for ACLF

Antiviral strategies in ACLF HBV reactivation: The presence of high HBV DNA (≥10 (5) copies/ml/or≥ 2 × 10 (4) IU/ml) is highly sensitive and specific for the diagnosis. Early and rapid reduction in HBV DNA is the essence of therapy. Several studies have indicated that if the reduction in DNA of >2 logs could be achieved within 2 weeks, the survival could be improved. This could be related to the suppression of hepatocellular necrosis and cytokine release. Besides patients who present with ACLF, it is worthwhile that prophylactic therapy should be considered for HBsAg-positive patients undergoing chemotherapy. There is insufficient data to recommend antiviral therapy for HBsAg- negative and antiHBc-positive patients with possible reactivation of occult HBV infection.

- Nucleos(t)ide analogs should be started immediately in all HBV-infected patients at presentation while waiting for confirmation by HBV DNA level. Potent antiviral drugs, such as tenofovir, entecavir, or telbuvidine, should be used
- Assessment of reduction in HBV DNA level at day 15 after nucleos (t) ide analogs is encouraged; if < 2 log reduction, it suggests poor prognosis

Liver transplantation

Both deceased and living donor transplants are viable and very useful options with very good results. Liver transplantation results from the East in patients with HBV reactivation have shown successful 5year survival above 90 %.

- No validated criteria and scoring system for early and correct

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identification of patients with ACLF who would benefit from early liver transplantation
- MELD could be used for patient selection, needs evaluation in ACLF
- ACLF patients with MELD >30 should be considered for urgent transplantation
- Patients with HBV reactivation with intermediate MELD should be assessed for early transplant if cirrhosis, bilirubin >10 mg/dL, PT <40 %, and platelet <100 × 10 /L
- Organ failure per se should not be a contraindication for transplantation, except if cardiac or pulmonary support needed or rapidly progressing organ failure at day 4 or 7
- LDLT/DDLT attain satisfactory long term survival, even in ACLF patients with high MELD score

Liver dialysis and replacement therapy in ACLF

Extracorporeal liver support therapies are used to bridge the liver until recovery or liver transplantation in patients with ALF and ACLF. Various randomized controlled trials in patients with ACLF have shown improvement in hepatic encephalopathy, hepatorenal syndrome, circulatory dysfunction, and immune dysfunction without improvement in transplant free survival. More recently, studies have shown that ALS could be an effective form of bridging therapy in patients with ACLF with high MELD scores awaiting liver transplantation and many believe it is a futile exercise in the absence of liver transplant.

Conclusion

ACLF is a devastating syndrome since it remains a highly prevalent, life-threatening disease, which is clinically, pathophysiologically and prognostically a distinct entity from a mere decompensation of cirrhosis. The purpose of this review is to demonstrate the differing ways ACLF is characterized and define the natural course of patients with ACLF especially as it relates to management of cirrhotic patients on the transplant waiting list and its impact on liver transplantation outcomes.

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